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The European Journal of Endocrinology Prize Lecture

The European Journal of Endocrinology Prize is awarded to a candidate who has contributed significantly to the advancement of knowledge in the field of endocrinology through publication. This year's recipient is Professor Filip K. Knop who will receive his prize and deliver his lecture as part of the ECE 2018 Opening Ceremony on Saturday 19 May 2018. Further information on the prize can be found at https://www.ese-hormones.org/grants-and-awards/awards/.

Filip K. Knop, MD PhD, is a consultant endocrinologist, professor of endocrinology and head of Clinical Metabolic Physiology at Steno Diabetes Center Copenhagen, University of Copenhagen, Denmark. Prof. Knop has been involved in diabetes research since his fellowship at The Distinguished Gifford Laboratories for Diabetes Research, University of Texas, Southwestern Medical Center in Dallas in 1999 where he was supervised by Professor Christopher B. Newgard. Filip K. Knop's research, for which he has received a number of grants and honours (e.g. named 'Rising star' by the European Association for the Study of Diabetes), centres on the pathophysiology of type 2 diabetes, obesity, regulation of appetite and food intake, and the therapeutic role of incretins. He is particularly interested in the integrative role of the gut and the liver in human (patho)physiology and has authored >250 scientific publications. He serves as a referee for several international journals including The Lancet, British Medical Journal, Diabetes and Diabetologia and he is a member of numerous professional societies and committees.

The European Journal of Endocrinology Prize Lecture

EJE1

A gut feeling about glucagon

Filip Knop
Denmark.

Hyperglucagonaemia (in the fasting as well as in the postprandial state) is considered a core pathophysiological component of diabetes and to contribute substantially to the hyperglycaemic state of diabetes. Hyperglucagonaemia is usually viewed upon as a consequence of pancreatic alpha cell insensitivity to the glucagon-suppressive effects of glucose and insulin. Since we observed that the well-known hyperglucagonaemic response to oral glucose in patients with type 2 diabetes is exchanged by normal suppression of plasma glucagon levels following isoglycaemic intravenous glucose administration in these patients, we have been focusing on the gut and gut-derived factors as potential mediators of diabetic hyperglucagonaemia. In a series of clinical experiments we have elucidated the role of gut-derived factors in diabetic hyperglucagonaemia and shown that glucose-dependent insulinotropic polypeptide promotes hyperglucagonaemia and that glucagon, hitherto considered a pancreas-specific hormone, may also be secreted from extrapancreatic tissues - most likely from proglucagon-producing enteroendocrine cells. Furthermore, our observation that fasting hyperglucagonaemia is unrelated to the diabetic state, but strongly correlates with obesity, liver fat content and circulating amino acids, has made us question the common 'pancreacentric' and 'gluco-centric' understanding of hyperglucagonaemia and led to the hypothesis that steatosis-induced hepatic glucagon resistance (and reduced amino acid turnover) and compensatory glucagon secretion mediated by increased circulating amino acids constitute a complete endocrine feedback system: The liver-alpha cell axis. This presentation summarises the physiological regulation of glucagon secretion in humans and considers new findings suggesting that the liver and the gut play key roles in determining fasting and postabsorptive circulating glucagon levels.

DOI: 10.1530/endoabs.56.EJE1

The Geoffrey Harris Prize Lecture

The prestigious Geoffrey Harris Prize is awarded to an established researcher in the field of neuroendocrinology and is the first of its kind in Europe. This year's recipient is Professor Christos S. Mantzoros, who will receive his prize and deliver his lecture as part of the ECE 2018 Opening Ceremony on Saturday 19 May 2018. Further information on the prize can be found at https://www.ese-hormones.org/grants-and-awards/awards/.

Christos S. Mantzoros, MD, DSc, PhD h.c. mult. is Professor of Medicine at Harvard Medical School and Boston University School of Medicine. He currently also serves as the Chief of Endocrinology, Diabetes and Metabolism at the Boston VA Healthcare System and the Director of the Human Nutrition Unit of the Division of Endocrinology Diabetes and Metabolism at Beth Israel Deaconess Medical Center. Dr. Mantzoros is also the director for the VA Boston Healthcare System fellowship program with Boston University Medical Center (BUMC). He has served as a board member, an advisor, or head of the scientific advisory boards of non-profit foundations as well as government and private entities. He also serves as the Editor-in-Chief of the journal Metabolism and is on the editorial board of several scientific journals worldwide. His research has resulted in more than 600 publications in Medline, more than 150 publications under the collaborative Look Ahead Research Group, more than 200 chapters and reviews and has received more than 49,000 citations and an H index of 114 with an i10 index of 421 (Google Scholar).

The Geoffrey Harris Prize Lecture

GH1

Geoffrey Harris Award
Christos Mantzoros
USA.

My research focuses on the interplay of brain and adipose tissue and the elucidation of the physiology, diagnostic, and therapeutic utility of adipokines and myokines. We defined the central role these compounds play in normal physiology and pathophysiology of several diseases in humans, with the notion that such investigations will eventually lead to new treatments for metabolic and cardiovascular disease. We have also studied in-depth the role of leptin in the brain, defining the neuroendocrine and functional brain deficits in hypoleptinemia and how these, as well as deficits in fertility and bone physiology, can be corrected by the administration of leptin, which in turn acts centrally to effect these changes. This work, in addition to his work on leptin in lipodystrophy, contributed greatly to the FDA approval of leptin in the United States and Japan, with other approvals forthcoming. Additionally, we have worked on the development of INT131, a selective PPARγ modulator, which increases levels of adiponectin. This compound was recently approved by the FDA for phase III clinical trials. In light of adiponectin's role in neuroendocrinology and metabolism, this drug is another useful translational tool that will undoubtedly lead to much-needed therapeutic applications. Extending our previous work in the field of neuroendocrinology, we are currently investigating the effect of liraglutide, a GLP-1 agonist, and lorcaserin, a serotonin 5HT-2c receptor agonist on appetite regulation and energy homeostasis. Results from these on-going studies show that liraglutide decreases attention to high fat or high calorie foods through actions in the brain, and we identified GLP-1 receptors in human brains for the first time. These exciting results will set the foundation for decoding the pathophysiological- neuroendocrine mechanisms involved in obesity and energy homeostasis, support the establishment of effective therapies for obesity, and help to identify the individuals who will benefit from them.

DOI: 10.1530/endoabs.56.GH1

European Hormone Medal Lecture

The European Hormone Medal is awarded to an international scientist who has made significant contributions to the field of basic or clinical endocrinology. This year's recipient is Professor Ilpo Huhtaniemi who will receive his prize and give his lecture as part of the European Congress of Endocrinology (ECE), beginning on the 19 May 2018. Further information on the prize can be found at https://www.ese-hormones.org/grants-and-awards/awards/.

Ilpo Huhtaniemi, MD, PhD, is Emeritus Professor of Reproductive Endocrinology at Imperial College London, and Professor of Physiology at University of Turku, Finland. His research interests include clinical and basic reproductive endocrinology, in particular the function of gonadotrophins and male reproduction, as well as male contraception, hormone-dependent cancer, and the endocrinology of ageing. He has authored about 700 peer-reviewed research articles and reviews. He was Chief Editor of Molecular and Cellular Endocrinology in 1999–2017. He is recipient of several awards, including the fellowship of The Academy of Medical Sciences (UK), and Doctor Honoris Causa at the Medical University Lodz, Poland and University of Szeged, Hungary. He has held several positions of trust in international scientific organizations, e.g. Past President of International Society of Andrology and Member of the Executive Committees of EFES and ESE.

European Hormone Medal Lecture

EHM1

Unraveling Secrets of the Hypothalamic-Pituitary-Gonadal Axis

Ilpo Huhtaniemi
UK/Finland.

As in all fields of the life sciences, enormous development has taken place in my special field of interest, i.e. reproductive endocrinology, during the nearly 50 years' time that I have been involved in basic and clinical research. My research has focused to large extent on functions of the hypothalamic-pituitary-gonadal axis and more specifically on physiology and pathophysiology of gonadotrophin function. My research career in not unlike the human life-span, because my first studies concerned fetal endocrinology, demonstrating testosterone production in human fetal testis and its regulation by hCG. I thereafter focused on function of gonadotrophin receptors and their role on normal and pathological gonadal function. More recently, I have become interested in endocrinology of the aging male. One earlier study that I was pleased to be involved in was the discovery of the first inactivating mutation of FSH receptor in humans. We subsequently continued on the line of unraveling the molecular mechanisms involved in mutations of gonadotrophin and their receptor genes by producing several genetically modified mouse models (transgenic and knockout) for disturbances of gonadotrophin function. These studies unraveled novel functional features of gonadotrophins in the regulation of gametogenesis, as tumor promoters, in extragonadal functions, and concerning molecular aspects of their actions. Finally, my participation in the European Male Ageing Study (EMAS) has widened understanding of the physiology and pathophysiology of male aging – an appropriate way to round up the career for an aging reproductive scientist. In this lecture I will review some of our findings along the hypothalamic-pituitary-gonadal axis that have furthered our knowledge about this fascinating regulatory cascade, in addition to providing me with some intellectual satisfaction of discovery.

DOI: 10.1530/endoabs.56.EHM1

Clinical Endocrinology Trust Lecture

The Clinical Endocrinology Trust (CET) Award is given for clinical research that addresses aspects of endocrinology at the forefront of clinical practice. This year's recipient is Professor Philippe Chanson who will receive his prize and give his lecture as part of the European Congress of Endocrinology (ECE), beginning on the 19 May 2018. The award is sponsored by the Clinical Endocrinology Trust and further information can be found at https://www.ese-hormones.org/grants-and-awards/awards/.

Philippe Chanson is Professor of Endocrinology at University Paris-Sud and Head of the Department of Endocrinology and Reproductive Diseases at Bicêtre's Hospital (Assistance Publique-Hôpitaux de Paris), where he coordinates a National Center for Rare Pituitary Diseases. He also leads the Bicêtre HCP for Endo-ERN. He is a member of several scientific societies including Endocrine Society, European Society of Endocrinology, European Neuroendocrine Association (ENEA), Pituitary Society, Growth Research Society and French Society of Endocrinology. He participates actively to numerous Consensus Groups organized by these Societies. He is the General Secretary of the « French Pituitary Club » and past Treasurer of ENEA.
His main interest is in Neuroendocrinology: pituitary adenomas including acromegaly, Cushing's disease; and Reproduction (gonadotropic function and disorders) which are his main clinical research themes. He conducts his basic research in INSERM U 1185 on effects of GH on kidney and on pituitary tumorigenesis. He has served the Boards of Clin Endocrinol, J Clin Endocrinol Metab, Endocrine, J Endocr Soc and is now in the Editorial Board of Pituitary. He is the author or co-author of more than 260 original peer-reviewed contributions and many invited reviews or book chapters.

Clinical Endocrinology Trust Lecture

CET1

Growth Hormone: not too much… not too less..!

Philippe Chanson
France.

Growth hormone (GH) and insulin-like growth factor-I (IGF-I) have important metabolic actions. GH/IGF-I excess and GH deficiency are each associated with 'opposing' comorbidities that often mirror one another. Cardiac and vascular comorbidity demonstrates that 'too much' may be as bad as 'too little'. An association between acromegaly and increased cardiac mortality has long been claimed. This was based on epidemiological studies of patients treated a long time ago, when the current therapeutic tools were not available and radiotherapy was widely used. Recent epidemiological studies and data from acromegaly registries show no excess mortality and that cardiovascular disease is not the leading cause of death. This is thanks to effective treatment of acromegaly and aggressive management of comorbidities (diabetes, hypertension, lipid disorders). Observations resemble those in the background general population. In contrast, the clinical features of hypopituitarism with GH deficiency are more like those of the metabolic syndrome. This may explain why patients have an increased cardiovascular and cerebrovascular risk. GH treatment improves cardiovascular risk factors and is associated with a decreased incidence of cardiovascular (but not cerebrovascular) events in some studies. It also seems to be associated with a reduction in all-cause mortality in both sexes, but particularly in males, who attain the level of the general population. Thus, according to our homeostatic model, the GH/IGF-I axis follows the general rule that in medio stat virtus or 'virtue stands in the middle'!

DOI: 10.1530/endoabs.56.CET1

Plenary Lectures

Contraception: Past and future

PL1

Contraception: past, present, and future

Philippe Bouchard
France.

50 years after the approval in the USA of the first oral contraceptive, it is quite remarkable that this considerable medical advance, may be the greatest medical discovery in the last century, the combined pill, which replaced condoms and unreliable natural methods, is still a matter of controversy. Recently, fear for hormones is more and more common in women in relation with the pill scares observed in UK and in France, and in relation with the media noise on Endocrine disruptors. However, it must be remembered that 40% of all pregnancies are still undesired, thus leading to a large number of pregnancy terminations, and also in the maternal consequence of unintended pregnancies. The pill is still a method of choice, safe and efficient, provided women are selected with exclusion of high risk individuals of some methods. Contraception is not only important for individual and couples but play an important role in population dynamics. Further long acting contraception methods such as implants or IUS, and OCs are now available, while new estrogens are also on the market or near commercialization such as Estetrol containing pills. Implants and vaginal rings, are safe and well tolerated, and IUS and IUDs are more and more user friendly. The most recent and remarkable developments are the progress in Emergency contraception using Ulipristal Acetate, a very efficient and risk free method. Finally, the recent discovery of beneficial effects of progestins in particular on brain function are now clear and provides a new advantage. Finally, while the pill is less used in women, the last progress come from the development of male contraception methods. Following the failure of the development of methods by the Pharma industry, new methods supported by NIH, using DMAU, dimethylandrolone undecanoate oral pill, Nestorone-testosterone gel, NES implants, are in development and preliminary results show a remarkable tolerance and a good efficacy. These methods produce a very high rate of extreme oligospermia, and are very promising for a near availability on the market. In addition, research into the development of non-hormonal contraception for men is progressing in several laboratories. The non-hormonal approach aims at inducing reversible infertility without interfering with hormones secreted by the hypothalamus, pituitary gland, and testis. New research target spermiogenesis, differentiation, maturation of sperm, or factors inhibiting sperm motility. Antagonists to the testis-specific Bromo Domain Protein, or to the retinoic acid receptors, involved in meiosis, proved effective in inhibiting spermatogenesis. Adjudin or H2-gamendazole, two modified lonidamine derivatives, cause premature spermiation and infertility. Eppin (epididymal protease inhibitor) secreted by Sertoli cells is also a potential target. Anti-Eppin antibodies inhibit human spermatozoa motility. Blocking CatSper (cationic channel of sperm), a novel and complex ion channel mediating $Ca2^{+}$ entry in sperm flagellum, or the sperm-specific glyceraldehyde-3-phosphate dehydrogenase (GAPDS) result in reduced sperm motility. New formulations designed to deliver specifically such antagonists are also under early testing. Contraception is a treasure, all the methods available should eradicate the need for abortions, and the most recent methods are safe and user friendly. Research in particular on methods impacting on oocyte fertilization should continue. Novel technologies include research on nanoparticles, microarray patch, drug-eluting fibers, as well as improved long-acting reversible contraceptives including new intra uterine systems, novel design of vaginal rings, and microchip technology. Research on genomics and proteomics is needed to define new targets for future development. Continuing funding is absolutely needed. Unmet needs in family planning remain a significant challenge worldwide. As a result, women continue to bear the burden of more than 85 million unplanned pregnancies and 48 million abortions each year. Novel male contraceptives could play a meaningful role in averting unintended pregnancies especially in settings where novel methods can attract new contraceptive users.

DOI: 10.1530/endoabs.56.PL1

Bone regulates the Brain

PL2

Bone Regulates the Brain to Control Appetite

Stavroula Kousteni
USA.

The discovery of the multiple endocrine functions of bone on the control of energy metabolism raised the question of whether several bone-derived hormones may exist that contribute to the regulation of metabolic functions such glucose tolerance, insulin sensitivity and energy expenditure, or whether they elicit a yet unanticipated endocrine function.. In response to this question a known hormone with a previously unidentified action was found to mediate a new metabolic function of bone: appetite. We have found Lipocalin 2 (LCN2), a previously thought adipokine, as an osteoblast-enriched secreted protein regulating food intake. Inactivation of Lcn2 specifically in osteoblasts (Lcn2osb-/- mice) increases blood glucose levels fat mass and body weight, decreases serum insulin and leads to glucose intolerance and insulin resistance. These effects result mainly from a 23.7% increase in food intake which is first detected at 3 weeks of age and remains elevated thereafter. In contrast, inactivation of Lcn2 in adipocytes has no effect on any of metabolic parameters. LCN2 is secreted by osteoblasts, crosses the blood brain barrier (BBB), binds to the melanocortin 4 receptor (MC4R) in the paraventricular and ventromedial neurons of the hypothalamus and activates the MC4R-dependent anorexigenic pathway. In addition, LCN2 has a physiological role in the regulation of feeding. LCN2 serum levels in fasted and refed wild type mice increased 3-fold after refeeding. This was to be due to a 1.6 fold increase in Lcn2 expression by osteoblast osteoblasts since Lcn2 expression by adipocytes was not altered. Intraperitoneal administration of recombinant LCN2 to fasted Lcn2-/- mice immediately after refeeding suppressed food intake within 1 hour and decreased body weight gain within 2 hours as efficiently as in WT mice. These observations identify Lcn2 as an osteoblast-derived anorexigenic hormone and regulation of appetite as a novel endocrine function of bone.

DOI: 10.1530/endoabs.56.PL2

The wonder world of GnRH neurons

PL3

The wonder world of GnRH neurons - cracking the pulse generator

Allan Herbison
New Zealand.

The gonadotropin-releasing hormone (GnRH) neurons are key cells regulating fertility in all mammals including humans. They release GnRH in an episodic manner to drive the pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone critical for gonadal function. Remarkably, the GnRH neurons are not born in the brain but arise from the nose and migrate into the brain during early embryogenesis. This unique origin engenders a variety of unusual and unique properties in the GnRH neuron. Foremost is their scattered location throughout the basal forebrain from where they send projections to the median eminence at the base of the brain to release GnRH into the pituitary portal system. Again, remarkably, this projection is not an axon but a blended process called a 'dendron' with unique properties of both dendrites and axons. Decades of study have focused upon defining the special characteristics of the GnRH neuron that may underlie their ability to generate pulsatile GnRH secretion. By and large, this has been unsuccessful. The discovery in 2003 of key role for kisspeptin in human fertility and pulsatile gonadotrophin secretion provided an important clue suggesting that an external neuronal input to the GnRH neuron may be critical for pulsatility. Since that time, studies in genetically-manipulated mouse models have addressed the role of kisspeptin neurons in pulse generation using a range of cellular approaches combined with the latest optogenetic techniques enabling high precision investigations *in vivo*. Together, these studies have identified the GnRH pulse generator as being a population of kisspeptin neurons located in the hypothalamic arcuate nucleus that exhibit synchronized episodes of activity which activate the GnRH neuron dendron to evoke pulsatile LH secretion. This represents an unusual and unexpected mechanism of generating pulsatile hormone secretion and opens up new possibilities for the manipulation of fertility in the clinic.

DOI: 10.1530/endoabs.56.PL3

The Retina as a Window for Exploring the Brain in Diabetes

PL4

The Retina as a Window for Exploring the Brain in Diabetes

Rafael Simó
Spain.

Evidence is accumulating that type 2 diabetes (T2D) is associated with cognitive impairment and dementia. In fact, numerous epidemiological studies have demonstrated that T2D patients have a significantly higher risk of developing neurodegenerative diseases and, in particular, Alzheimer's disease (AD). In clinical practice there are no reported phenotypic indicators or specific examinations to identify T2D patients at risk of developing AD. This gap should be urgently bridged given the rise in the global prevalence of T2D with cognitive

impairment and in anticipation of improved treatments for the prodromal stages of AD. Diabetic retinopathy (DR) is one of the most frequent diabetic complications and the leading cause of visual impairment and preventable blindness. Although traditionally DR has been considered a microvascular disease, there is emerging evidence that neurodegeneration is an early pathogenic event. In fact, the American Diabetes Association has recently defined DR as a highly specific neurovascular complication. Since the retina is ontogenically a brain-derived tissue and it has been suggested that it may provide an easily accessible and non-invasive way of examining the pathology of the brain. Therefore, it could be postulated that in patients developing neurodegeneration of the brain there is a co-occurring neurodegenerative process in the retina ('the eye as a window of the brain'). In this regard, we have recently suggested that retinal sensitivity assessed by microperimetry could be a useful biomarker for identifying patients with T2D who are at risk of developing AD. This nested case-control pilot study will be commneted on. We have recently found by proteomic analysis of human retinas from diabetic patients several genuine pathways triggered in the brain of neurodegenerative diseases. These findings suggest that the study of neurodegeneration in the diabetic retina could be useful to further understand the neurodegenerative processes that occur in the brain of persons with diabetes.

DOI: 10.1530/endoabs.56.PL4

The link between insulin and fatty liver

PL5

The link between insulin and fatty liver

Gerald Shulman
USA.

Ectopic lipid deposition in liver and skeletal muscle plays a major role in the pathogenesis of insulin resistance and type 2 diabetes (T2D). Furthermore, nonalcoholic fatty liver disease (NAFLD) is a major predisposing factor for nonalcoholic steatohepatitis (NASH) and hepatocellular cancer and is an independent risk factor of cardiovascular disease. Understanding the cellular and molecular mechanisms by which ectopic lipid promotes insulin resistance in liver and identifying the key lipid mediators in this process is therefore of great interest. Recent studies have identified diacylglycerols, as a molecular trigger for lipid-induced hepatic insulin resistance through activation of PKC-epsilon (PKCe) resulting in phosphorylation of insulin receptor Thr1160 and inhibition of insulin receptor kinase activity. In addition, alterations in hepatic acetyl-CoA, an allosteric activator of pyruvate carboxylase, have been shown to mediate insulin suppression of hepatic gluconeogenesis as well as promote increased rates of hepatic gluconeogenesis in patients with poorly controlled T2D. In support of these mechanisms recent studies have demonstrated the potential utility and safety of liver-targeted hepatic mitochondrial uncoupling as a novel therapeutic approach to treat NAFLD, NASH and T2D in rodent and non-human primates and reverse hepatic insulin resistance and diabetes by decreasing hepatic DAG-PKCe activity and reducing hepatic acetyl-CoA content.

DOI: 10.1530/endoabs.56.PL5

Does therapy for thyroid dysfunction decrease mortality?

PL6

Does therapy for thyroid dysfunction decrease mortality?

Laszlo Hegedüs
Denmark.

Background
Meta-analyses have questioned whether mortality is increased in hyper- and hypothyroid individuals, and if so the magnitude. This is mainly due to inadequate size of study populations, differences in study design and participant characteristics, lack of control for confounders and whether the participants are treated.
Materials
Using record-linkage data from nationwide Danish health registers, and after adjustment for preexisting morbidity, a 22–42% excess mortality was demonstrated in hyperthyroidism, higher in Graves' disease than in toxic nodular goiter. In hypothyroidism the excess mortality was 23%. In both phenotypes there was an increased risk of being diagnosed with a number of morbidities, especially cardiovascular diseases. For both hyper- and hypothyroid individuals there was an increased risk - 51 and 140%, respectively - of being diagnosed with psychiatric diseases (psychosis, depression and anxiety). Both hyper- and hypothyroidism was associated with an increased risk - 88 and 89%, respectively - of receiving disability pension. The above studies lacked adequate thyroid function variables and data on therapy. In a register-based Danish cohort of ca. 235.000 individuals offering such data, and followed for a median of 7 yr., increased mortality (23%) in untreated but not in treated hyperthyroid patients was demonstrated. Hazard ratio for mortality was around 1.12 for every 6 months of decreased TSH, whether individuals were treated or not. In the same cohort, untreated hypothyroid individuals had an excess mortality of 46%, which was at large uninfluenced by age (below or above 65 yr.) and severity (mild or overt) of hypothyroidism. Mortality was increased by 5% for every 6 months of increased TSH.
Conclusions
Mortality is increased in both hyper- and hypothyroidism. Cumulative periods of abnormal TSH increases mortality in both treated and untreated individuals, suggesting that not lack of therapy but lack of maintaining euthyroidism may drive excess mortality.

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Metabolic control of longevity

PL7

Anti-obesity effect in mice and monkeys of partial inhibition of PI3Kα

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Spain.

Partial inhibition of PI3K is one of the best-validated and evolutionary conserved manipulations to extend longevity. PI3K is a master regulator of anabolism and the best validated beneficial effects of reduced PI3K are related to metabolism and include increased energy expenditure, reduced nutrient storage, and protection from obesity. We have found that a dual chemical inhibitor of the α and δ PI3K isoforms (CNIO-PI3Ki) reduces obesity in mice and monkeys, without evident toxic effects after long-term treatment. Similar effects have been observed with the pan-PI3K inhibitor GDC-0941.The doses used only achieved a mild inhibition of PI3K activity and therfore did not result in significant hyperglycemic peaks. More recently, we have found that the selective PI3Kα inhibitor BYL-719 (also known as alpelisib) also has anti-obesity activity. This is in contrast to the selective PI3Kδ inhibitor GS-9820 (also known as acalisib), which had no effect. However, the dose of BYL-719 required to reduce obesity was 10-times higher than the equivalent dose of CNIO-PI3Ki, which could suggest that simultaneous inhibition of PI3K α and δ is more effective than single inhibition of the α isoform. In summary, we conclude that inhibition of PI3Kα is sufficient to reduce anabolism, increase energy expenditure and reduce obesity, and suggest that concomitant PI3Kδ inhibition could play an auxiliary role.

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Symposia

Predicting events in autoimmune thyroid disease

S1.1

The THEA score in familial thyroid dysfunction. Predictive factors of autoimmune thyroid disease

Grigorios Effraimidis
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AutoImmune Thyroid Disease (AITD) is, nowadays, generally considered to be a complex multifactorial entity, in which the interplay between genetic and environmental factors results in the expression of the disease. Genetic predisposition plays a major role in the pathogenesis of AITD, as siblings and other family members of AITD patients are at increased risk for AITD. Then, how can we, as physicians, answer the question of our AITD patients 'will my children also get the disease?'. A predictive score for the development of overt hypothyroidism or hyperthyroidism within 5 years was composed, based on the findings from a prospective observational study of the 'Amsterdam AITD cohort'. The score is called the Thyroid Events Amsterdam or THEA score. The cohort consisted of healthy first- or second- degree female relatives of patients with AITD who were observed for 5 years. Thyroid function tests, family history and exposure to some environmental insults at study entrance were put in a model for the calculation of the score. The numerical THEA score predicts events by weighing the three independent risk factors: TSH, TPOAb and family background. The higher the THEA score, the higher the risk of developing overt thyroid dysfunction within a period of 5 years. During the presentation, I aim to give a description of the development of the THEA score, its clinical applicability, a brief report of the recent clinical studies regarding the factors which influence the development of AITD and, finally, what the future holds in the field of the prediction of developing AITD.

DOI: 10.1530/endoabs.56.S1.1

S1.2

IgG4 related thyroid autoimmune disease

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Italy.

IgG4-related disease (IgG4-RD) is a fibro-inflammatory, immune-mediated, systemic disease usually presenting with tumefactive lesions and a subacute onset mimicking malignancy. A subset of autoimmune thyroid pathologic conditions can be incorporated in the spectrum of IgG4-RD. In some cases of Hashimoto's Thyroiditis (HT) a rich IgG4-positive plasma cell infiltration has been described, and a marked storiform fibrosis is typical of the fibrotic variant of HT (FVHT) and of Riedel's Thyroiditis (RT). In addition, the serum levels of IgG4 have been demonstrated to correlate with activity and severity of Graves' orbitopathy (GO). Finally, IgG4-RD should be considered in the differential diagnosis of Graves' like orbitopathy. The pathogenesis of IgG4-related thyroid diseases is poorly understood, but an autoimmune process resulting from genetic and environmental factors is hypothesized to play a pivotal role. Whether or not IgG4 have a direct pathogenic effect still remains to be ascertained, because infiltrating IgG4-positive plasma cells might only represent an epiphenomenon. The diagnostic criteria for specific IgG4-related thyroid diseases rely on histology. Thus, tissue biopsy is mandatory for a correct clinical assessment. Lympho-plasmacytic infiltrate, storiform fibrosis and obliterative phlebitis are the histologic hallmarks that confirm the clinical suspicion. The measurement of serum IgG4 levels may contribute to the diagnostic workup, and specific cut-offs have been propose in thyroid IgG4-RD. However, IgG4 serum negative patients do exist. Thus, the presence of high levels IgG4 in serum is not necessary to diagnose thyroid IgG4-RD. On the other hand, monitoring serum IgG4 levels can demonstrate treatment response or disease activity. Management options are both medical and surgical, depending on which condition has been diagnosed. Generally, glucocorticoids are the first line therapy and allow reducing the progression of the disease, while surgical management has been performed only in rare cases.

DOI: 10.1530/endoabs.56.S1.2

S1.3

New scores for the prediction of Graves' disease

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Serbia.

After treatment, hyperthyroidism will relapse in approximately half of the Graves' diseases patients, and clinically relevant orbitopathy will develop in about 25% of the diseased. Therefore, predicting who will relapse or develop orbitopathy is both clinically important and contributes to understanding of the pathophysiology of the disease. To predict the risk of recurrence of hyperthyroidism, before the start of antithyroid drug therapy, GREAT (based on clinical markers) and GREAT+ (based on clinical and genetic markers) scores were proposed. GREAT score is based on age, free thyroxin (fT4) concentration, thyrotropin-binding inhibitor immunoglobulin (TBII) concentration, and goitre size (according to the World Health Organization). GREAT+ score also includes HLA polymorphisms (DQB1-02, DQA1-05, DRB1-03) and PTPN22 C/T polymorphism. Higher score was correlated with the greater risk of hyperthyroidism relapse. Recurrence of hyperthyroidism occurred in 16% of the patients with the GREAT score 0–1, 44% when GREAT score is 2–3, and in 68% of the patients with the GREAT score 4–6. GREAT+ score further improved classification. Only 4% of subjects with GREAT+ score 0-2, had hyperthyroidism relapse, while 84% with GREAT+ score 7–10 relapsed. Independent, external validation of the GREAT score proved good validity of this score to predict disease relapse. To predict development or progression of Graves' orbitopathy in patients with Graves' hyperthyroidism PREDIGO score has been recently proposed. This score is based on clinical activity score (0 vs. $>$ 0), TBII concentration, duration of hyperthyroid symptoms before therapy, and smoking. This score has very good negative predictive value (0.91). Predictive scores allow choosing appropriate therapy for the patients (drugs, surgery, radioactive iodine), thus enabling to prevent or minimize adverse effects of the chosen therapy.

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Salt & Sweet

S2.1

Hyponatremia and mortality: moving beyond associations

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The Netherlands.

Acute hyponatremia can cause death if cerebral edema is not treated promptly. Conversely, if chronic hyponatremia is corrected too rapidly, osmotic demyelination may ensue, which also potentially is lethal. However, these severe complications of hyponatremia are relatively uncommon and often preventable. More commonly, hyponatremia predicts mortality in patients with advanced heart failure or liver cirrhosis. In these conditions, it generally is assumed that hyponatremia reflects the severity of the underlying disease rather than contributing directly to mortality. The same assumption holds for the recently reported associations between hyponatremia and mortality in patients with pulmonary embolism, pulmonary hypertension, pneumonia, and myocardial infarction. However, recent data suggest that chronic and mild hyponatremia in the general population also are associated with mortality. In addition, hyponatremia has been associated with mortality in long-term hemodialysis patients without residual function in whom the underlying disease cannot be responsible for hyponatremia. These new data raise the question of whether hyponatremia by itself can contribute to mortality or it remains a surrogate marker for other unknown risk factors. In this presentation I will review hyponatremia and mortality and explore the possibility that hyponatremia perturbs normal physiology in the absence of cerebral edema or osmotic demyelination.

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S2.2

Hereditary diabetes insipidus

Jonas Rutishauser
Switzerland.

Background
Families with inherited forms of diabetes insipidus (DI) have been described since the mid 19th century. Depending on the involved gene, the disorder is transmitted in autosomal dominant, autosomal recessive, or X-linked fashion.

Nephrogenic DI
Patients typically have a severe phenotype manifesting shortly after birth. They are most often males with X-linked disease due to variations in the vasopressin V2 receptor (AVPR2) gene. Rarely, variations in the aquaporin-2 (AQP2) gene underlie autosomal recessive or dominant transmission. Mutant proteins are functionally deficient and mostly retained in intracellular compartments.
Neurogenic DI
Symptoms of autosomal dominant familial neurohypophyseal DI (ADFNDI) start subtly months to years after birth, gradually increasing in severity. ADFNDI is caused by variations in the vasopressin (AVP) gene. Mutant proteins form amyloid-like aggregations and are retained in the endoplasmic reticulum. Rarely, autosomal-recessive neurohypophyseal DI results from AVP variations causing impaired binding to the AVPR2.
Diagnosis and treatment
Clinical testing by water deprivation (with or without infusion of hypertonic saline) is feasible but should be performed with caution, particularly in nephrogenic DI, since children may rapidly become severely dehydrated. Measurement of circulating copeptin levels during the test procedure facilitates differential diagnosis, and MRI of the hypothalamic/pituitary region may show abnormal findings. Direct genetic testing is indicated if a DI pedigree is present, or in patients with early-onset idiopathic DI even in the absence of a family history. Treatment strategies in hereditary DI follow those in non-hereditary disease. Pharmacological chaperones to promote rescue and membrane insertion of intracellularly retained AVPR2 molecules are not yet in clinical routine.
Conclusion
A family history of DI should prompt the correct diagnosis, but de novo mutations have been described as well. Mutational analysis is preferable over functional testing, particularly in children and in hereditary nephrogenic DI, where dehydration may become severe.

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S2.3

Going hedonic – the role of FGF21 in the preference for sweet and alcohol

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Denmark.

Human health is influenced by diet composition as well as total energy consumption; however, the circuits that control hunger and food-seeking in general are better understood than the interoceptive mechanisms that lead to consumption of specific nutrients, though the latter may impact both total energy intake and the health quality of food choices. Thus, a better understanding of the biological basis of palatable nutrient appetite is needed to improve diet quality and human health in modern food environments. However, food preferences are partly heritable. Genome-wide association studies have correlated genetic variants at the FGF21 locus with relatively increased carbohydrate and decreased protein and fat intake. FGF21 is a liver-derived hormone that exerts a range of metabolic effects in rodents and non-human primates in both physiological and pharmacological contexts. We recently found that carriers of a genetic variant in FGF21 had higher intake of candy and sweet food. Recent work furthermore clarifies the role of FGF21 in relation to alcohol intake in human genetic studies, human physiological studies and rodent mechanistic investigations. Similarly, recent genetic studies of the UK Biobank clarify the long-term impact of naturally occurring FGF21 variants on obesity and cardiovascular health. Further studies will seek to elucidate other genetic and hormonal factors involved in regulation of 'the sweet tooth' and other hedonic behavioural habits.

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Bile Acid & Microbiota
(*Endorsed by Endocrine Connections*)

S3.1

Crosstalk between bile acids and the gut microbiota – influence on host metabolism

Annika Wahlstrom
Sweden.

Bile acids are endocrine molecules that in addition to facilitating the absorption of fat-soluble nutrients regulate numerous metabolic processes, including glucose, lipid, and energy homeostasis. The actions of bile acids are mediated through specific bile acid-activated nuclear and membrane bound receptors such as farnesoid X receptor (FXR) and G protein-coupled receptor 5 (TGR5). Bile acid signaling is modified by interactions with gut bacteria which metabolize primary bile acids into secondary bile acids and thereby changes their affinity for their receptors. FXR and TGR5 have become major targets for studies of metabolic diseases and it is clear that the microbiota can modulate signaling through both FXR and TGR5 via modifications of bile acids. Conversely, bile acids can modulate gut microbial composition both directly and indirectly through activation of their receptors. To study the influence of microbiota and bile acid interactions on host metabolism we use germ-free mice that can be colonized with specific communities of bacteria. These mice are important tools but the interpretation and translation of results from mouse models must be done carefully since mice and humans have substantial differences in bile acid composition. The major primary bile acid in germ-free mice, TβMCA, is absent in adult humans and this bile acid function as an FXR antagonist. It has been shown that mice treated with antibiotics or Tempol have increased levels of TβMCA and are protected against diet- induced obesity and it was suggested that intestinal-specific inhibition of FXR was responsible for the beneficial effects. It has also been shown that a glycine-conjugated form of βMCA (GβMCA) improved metabolic phenotypes in obesity mouse models. On the other hand, it has also been shown that intestinal-specific activation of FXR with fexaramine protects against the development of obesity and was associated with increased thermogenesis and browning of adipose tissue. Furthermore, it has been suggested that some of the beneficial effects following bariatric surgery may be mediated by changes in gut microbiota, bile acid profile and FXR activation. Thus, targeting the interplay between microbiota, bile acids and FXR and/or TGR5 signaling seems to evolve as a promising avenue for the treatment of metabolic diseases but much more research is needed especially in humans.

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S3.2

Subclinical hypothyroidism is 'not' a disease (Contra)

Laura Gathercole
UK.

Thyroid diseases are common disorders. Globally, hypothyroidism is still frequently caused by iodine deficiency. In iodine sufficient areas, the most common cause of hypothyroidism is thyroid autoimmunity. Subclinical hypothyroidism is defined as elevated thyroid-stimulating hormone (TSH) levels with free thyroxine (fT4) estimates within the reference range. It is a common disorder that increases with age affecting up to 20% of the elderly, with a higher prevalence in women. Some prospective data have shown increased risks of coronary heart disease, heart failure, and cardiovascular mortality among affected adults, while others have not. Conflicting results have further been found on the association between subclinical hypothyroidism and cognitive impairment, depression and the risk of fractures. Overt hypothyroidism must be treated with levothyroxine. It is less clear if subclinical hypothyroidism requires replacement therapy. Screening for thyroid disease is not recommended by guidelines, but case finding based on specific criteria form general practice among endocrinologists. Since the condition is solely based on a laboratory diagnosis, there are many difficult factors to be aware of, including definition of the reference ranges for TSH and T4, both of which depend on laboratory and population factors; how measurements and interpretations of the laboratory tests for thyroid related hormones may be complicated by confounders due to medications, oral contraceptives, other diseases, non-thyroidal illness, and interference, and the difficulty of laboratory measurements to correct for these changes. Furthermore, the few randomized clinical trials have shown no beneficial effect from T4 treatment. Thus, due to current lack of evidence regarding the optimal treatment strategy in individuals with subclinical hypothyroidism, the best management of such persons is inclusion in trials, or to follow serum TSH values, which often normalize spontaneously. If TSH levels exceed 10 mIU/l, substitution might be considered, but even then, there is no direct evidence justifying treatment.

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S3.3

Bile acids and metabolic effects of bariatric surgery

Glenn Gerhard
USA.

Bariatric surgery, also known as metabolic surgery, has been shown through multiple clinical trials to result in superior efficacy and sustainability of weight loss and remission of diabetes after surgery in patients with extreme obesity

compared with intensive medical and lifestyle interventions. Although the metabolic effects of bariatric surgery have been observed for over 50 years, the primary molecular mechanisms underlying these effects are not well understood. A number of theories for the improvements in dysglycemia have been proposed, although accumulating evidence from both clinical observations and animal models supports a mechanistic role for alterations in bile acid levels. Bile acids have long been recognized as important mediators in the intestinal absorption of lipids but they also serve as ligands for the nuclear receptor farnesoid X receptor (FXR) and the cell surface receptor G protein–coupled bile acid receptor 1 (TGR5) which can have multiple and complex metabolic effects. The mechanisms by which post-bariatric changes in bile acids may affect glucose metabolism include regulating levels of fibroblast growth factor 19 (FGF19), glucagon-like peptide 1 (GLP-1), organ-specific effects, inflammation, and alterations in the gut microbiome. Due to their multiple and pleiotropic effects, the definitive role of bile acids in bariatric surgery is not yet known and will likely require randomized controlled clinical trials with specific bile acids and/or bile acid receptor modulators.

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Environmental effects on endocrine functions

S4.1

Developmental exposures to endocrine disrupting chemicals (EDCs) reprogram the epigenome to increase risk for hormone-dependent cancers and other diseases of adilthood

Cheryl Walker
USA.

While organisms have evolved to maintain the fidelity of their genome, the epigenome, in contrast, is inherently plastic, with extensive remodeling required during normal development. This epigenomic plasticity plays a role in preparing the developing organism for its adult environment. The epigenome is able to sense environmental cues, providing an opportunity for adaptive changes during development that can provide a later-life survival advantage. However, epigenomic plasticity also carries a liability. Adverse environmental exposures can disrupt the developing epigenome, and this developmental reprogramming can have life-long consequences, increasing risk for many diseases. Our work has revealed vulnerabilities in the epigenetic machinery targeted by environmental exposures, specifically endocrine disrupting chemicals (EDCs) that activate nuclear hormone receptors (NHRs). EDCs initiate non-genomic NHR signaling, activating kinases that disrupt the epigenetic machinery of developing cells by phosphorylating and altering the activity of the 'readers, writers, and erasers' of the epigenome. For example, the EDC bisphenol A (BPA) engages NHRs to activate PI3K/AKT signaling, phosphorylating the histone methyltransferase MLL to increase the active H3K4 histone mark at reprogrammed genes. This developmental reprogramming persists into adulthood, long after the initial environmental exposure occurred, resulting in changes in gene expression that increase disease risk. Interestingly, the impact of epigenetic reprogramming may be silent until challenged with another, later life exposure. For example, altered gene expression associated with an increase in active H3K4me1 or H3K4me3 marks may not occur until the promoters of reprogrammed genes are engaged by transcription factors, as is the case for hormone-responsive genes that become hyper-responsive to estrogen or testosterone. Alternatively, reprogramming of specific transcription factors, such as the transcription factor EGR-1 (which is activated by high-fat diet), can drive an exaggerated transcriptional response to high-fat diet in EGR-1 target genes. Thus, while epigenetic alterations induced by environmental exposures persist into adult life, their effect on gene expression may be conditional on later life events, which then reveal the impact of developmental reprogramming and promote adult onset disease.

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S4.2

Iodine deficiency in pregnancy and development of offspring

Malgorzata Trofimiuk-Muldner
Poland.

Iodine as the main component of thyroid hormones is an essential micronutrient for proper neurodevelopment. According to the WHO, its deficiency is the most common cause of preventable brain damage worldwide. Although most severe forms of iodine malnutrition have almost been eliminated, mild-to-moderate iodine deficiency is still very common, affecting approximately two billions people worldwide. Due to increased iodine requirements during gestation, iodine deficiency in pregnant women may be an issue even in populations considered iodine sufficient. Iodine deficiency is linked to the spectrum of health consequences defined as iodine deficiency disorders. Fetuses and young children are particularly vulnerable to deleterious effects of iodine malnutrition. It has been demonstrated in animal models that even mild iodine deficiency during gestation affects the brain cortex cytoarchitecture, glial development and myelinization in offspring, resulting in impaired learning capacity and behavioural changes. In humans consequences of severe iodine malnutrition, endemic cretinism included, have been well described. Prophylaxis with iodised oil in areas of severe iodine deficiency was proved to be effective in placebo-controlled randomised trials and resulted in a reduction of abortion, prematurity and stillbirth rates, as well as in decreased frequency of myxedematous cretinism. An evidence on the negative impact of mild-to-moderate iodine deficiency during pregnancy on children neurodevelopment is conflicting. Low iodine status in early pregnancy has been linked with lower verbal IQ and reading scores in the offspring (ALSPAC cohort), child language delay, behaviour problems, and reduced fine motor skills (Norwegian cohort) or lower spelling scores (Australian data). However, the association between children cognition and urinary iodine concentration during gestation has not been confirmed in a Dutch birth cohort, probably due to a low frequency of iodine deficiency in this group. The recently published results of randomised, placebo-controlled trial did not prove that iodine supplementation of mildly iodine deficient pregnant women influenced the neurocognitive development of their children.

DOI: 10.1530/endoabs.56.S4.2

S4.3

Environmental contaminants and endocrine disruption: the story of obesogens

Ana Catarina Sousa
Portugal.

According to the World Health Organization, obesity is one of the most important public health challenges of the 21st Century. There is no doubt that excessive calories intake and lack of exercise, are important factors, and that genetics plays a critical role. However, because genes in the population do not change fast enough, other causes must be involved. The involvement of other causes in the etiology of obesity is further strengthened by the fact that obesity is increasing sharply in young children, including babies for whom changes in exercise and eating patterns are unlikely to have occurred in the past decades. Furthermore, increases in body weight have also been reported in laboratory, domestic and wild animals. Such evidences strengthen the hypothesis that environmental factors are at play. In 2006, a new theory on the role of environmental contaminants in the etiology of obesity was proposed by Dr. Bruce Blumberg. This theory, known as the 'obesogen effect' postulates that environmental chemicals are able to promote obesity by increasing the number of fat cells and/or the storage of fat into the existing adipocytes. It was originally proposed for tributyltin (TBT), a potent endocrine disrupting chemical responsible for sex changes in marine gastropods. This endocrine disruptor was responsible *in vitro* and in experimental animals for the induction of adipogenesis; furthermore, prenatal exposure to TBT in mice was associated with adiposity later in life and in future generations. Since the obesogen theory was proposed, compelling evidences from *in vitro*, *in vivo* an epidemiological studies arose in the scientific literature and today several chemicals are considered as obesogens. This presentation will provide an overview of the implications of obesogens in metabolic disorders, while explaining the major classes of obesogenic compounds to which we are continuously exposed. Preventive measures to reduce exposure to these toxic chemicals will be described and the future perspectives in this exciting emerging field will be discussed.

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The role of sperm epigenome in fertility and inheritance

S5.1

The quality control of the male germline transcriptome

Noora Kotaja
Finland.

Accurate posttranscriptional regulation of gene expression is essential for the production of good quality spermatozoa. Active cell type-specific transcription, exceptionally diverse transcriptome, and finally, near-to-complete transcriptional

silencing during the late steps of spermatogenesis create a high demand for effective RNA regulatory mechanisms. Furthermore, RNAs packed inside spermatozoa can mediate epigenetic inheritance of father's acquired disorders, therefore having important implications on offspring health. Male germ cells are characterized by intriguing cytoplasmic ribonucleoprotein granules (germ granules) that participate in RNA regulation during spermatogenesis. By molecular characterization of germ granules in mice, we have revealed their central role in germline-specific RNA regulation. We have shown that in addition to the PIWI-interacting RNA (piRNA) pathway, germ granules in haploid male germ cells accumulate the components of the nonsense mediated mRNA decay (NMD) pathway. The NMD acts mainly by promoting the degradation of mRNAs undergoing premature translation termination, but it can also regulate the stability of a variety of other kind of substrates. Using germ cell-specific knockout mouse models, we have shown that the NMD-targeted RNA degradation is required for normal spermatogenesis, and has a critical role in the control of male germ cell's transcriptome. Altogether our results emphasize the significance of germ granule-associated RNA quality control mechanisms in the maintenance of male fertility.

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S5.2

Abstract unavailable

S5.3

Mechanisms of epigenetic inheritance through sperm: lessons we have learnt from model organisms

Tanya Vavouri
Greece.

Our lifestyle habits and environmental exposures are typically considered to affect only our health (with the exception of pregnant mothers). Nevertheless, there is epidemiological evidence from human studies that adverse health consequences can also be observed in offspring and grand offspring (e.g. Roseboom *et al*., Molecular and Cellular Endocrinology, 2001). The mechanisms of trans- or inter-generational epigenetic inheritance are currently not known. We, and others, have therefore turned to animal models to try to understand the mechanisms involved. During my talk I will present two animals models of inter- or trans-generational epigenetic inheritance and what we have learnt from them about how information is transmitted through the germline (Ost *et al*., Cell, 2014; Klosin *et al*, Science 2017).

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Precision Medicine for diabetes (*Endorsed by the European Journal of Endocrinology*)

S6.1

Pharmacogenetics in type 2 diabetes: precision medicine or discovery tool?

Jose Florez
USA.

In recent years technological and analytical advances have led to an explosion in the discovery of genetic loci associated with type 2 diabetes. However, their ability to improve prediction of disease outcomes beyond standard clinical risk factors has been limited. On the other hand, genetic effects on drug response may be stronger than those commonly seen for disease incidence. Pharmacogenetic findings may help to uncover new drug targets, illuminate pathophysiology, clarify disease heterogeneity, aid in the fine-mapping of genetic associations, and contribute to personalized or precision treatment. In diabetes, precedent for the successful application of pharmacogenetic concepts exists in monogenic forms of the disease, such as maturity onset diabetes of the young or neonatal diabetes. Whether similar insights will be produced for the common form of type 2 diabetes remains to be seen. With recent advances in genetic approaches, the successive application of candidate gene studies, large-scale genotyping studies and genome-wide association studies has started to generate suggestive results that may lead to changes in clinical practice. However, many potential barriers to the translation of pharmacogenetic discoveries to the clinical management of diabetes still remain. In this presentation, we will offer a contemporary overview of the field in its current state, identify potential obstacles, and highlight future directions.

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S6.2

Genetics can help to improve precision medicine in diabetes

Leif Groop
Sweden.

Diabetes is presently classified into two main forms, type 1 (T1D) and type 2 diabetes (T2D), but especially T2D is highly heterogeneous. A refined classification could represent an important step towards precision medicine in diabetes. We have carried out a data-driven cluster analysis in 15,000 'T2D-patients' aged 18 years or older from four different cohorts in Sweden and Finland using six variables (age at diagnosis, GAD-antibodies, BMI, HbA1c, HOMA2-B and HOMA2-IR) (Ahlqvist A *et al*. Lancet D&E, 2018). We thereby identified five replicable clusters of diabetes patients, three more severe forms and two milder forms with different patient characteristics and risk of diabetic complications. Cluster 1 included patients with severe autoimmune diabetes (SAID) and cluster 2 similarly insulin-deficient patients (SIDD) with poor metabolic control and high risk of diabetic retinopathy. Individuals in the most insulin-resistant cluster 3 (SIRD) had a 4-5-fold increased risk of diabetic kidney disease and hepatosteatosis compared to other clusters. The obesity-related cluster 4 (MOD) and age-related cluster 5 (MARD) showed a rather benign course of the disease. A criticism of cluster analyses is that they are rather subjective. To address this criticism we used genetics. One could think that cluster 2 included patients with misdiagnosed T1D, but this cluster did not show any association with T1D-associated HLA types. Cluster 3 showed association with SNPs associated with hepatosteatosis, whereas only clusters 4 and 5 showed clear association with established T2D SNPs. Till date we used a panel of 170 SNPs but are now performing GWAS with the hope to identify cluster-specific gene scores. In conclusion, we have been able to stratify patients into five subgroups predicting disease progression and development of diabetic complications more precisely than the current classification and we have used genetics to validate this clustering.

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S6.3

Precision Nutrition in Obesity: gene-diet interactions

Jose Ordovas
USA/Spain.

Background

Obesity, resulting from complex interactions between genetic and non-genetic factors, is one the most pressing health challenges in our society. Current treatments for losing weight based mainly on diet and exercise are mostly unsuccessful in the long term. Therefore, as an alternative to the current strategy of one-size-fits-all, a more individualized approach is proposed in which genotype data are used to personalize treatment and to optimize the results.

Objective
To inform about the state of the art research related to the influence of genetic variation in the modulation of the association between diet on obesity and weight-related measures.
Results
Most of the published research use observational studies to identify gene by diet interactions modulating obesity risk. Far fewer are randomized clinical intervention trials assessing short-term weight-loss or its long-term maintenance in relation to specific genotypes. The results of the studies undertaken to date show significant progress in identifying polymorphisms in genes related to obesity, the greatest body of literature being reported for the FTO gene. The results on gene-diet interactions in determining obesity phenotypes are very heterogeneous, with few exceptions such as the APOA2 locus with saturated fat and BMI. An important recommendation is to standardize the methodology for undertaking these studies. Furthermore, such lack of replication suggests undetected higher-level interactions and experimental caveats. One of the potential interactive factors is chronobiology. It has been shown that genetic variation in Clock-related genes is associated with obesity and with the response to dietary interventions aimed to lose weight. Moving forward, the integration of different high-throughput 'omic' techniques (i.e., genomics, epigenomics, and metabolomics) will provide the mechanistic basis to well-validated gene-diet interactions and add credibility to this area of nutrition research.
Conclusions
Despite substantial progress, the current evidence level of applying genotype data to obesity treatment is in its early stages. Nevertheless, prospects are promising.
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Expanding the spectrum of thyroid hormone use (*Endorsed by the European Journal of Endocrinology*)

S7.1

Triac: hormone, metabolite and drug.
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The prohormone thyroxine (T4) is the major product secreted by the thyroid gland, while most actions of thyroid hormone (TH) are initiated by binding of the active hormone 3,3′,5-triiodothyronine (T3) to nuclear receptors. The biological activity of TH is thus determined by the intracellular T3 concentration in target tissues, which depends on 1) the circulating concentrations of T4 and T3, 2) the activity of deiodinases catalyzing the conversion of T4 to T3 or to receptor-inactive metabolites, and 3) the activity of transporters which facilitate the cellular uptake and/or efflux of T4 and T3. As in many animals, administration of T4 or T3 induces the metamorphosis of the invertebrate amphioxus. However, T3 is incapable of stimulating the TH receptor in amphioxus in vitro, in contrast to the potent stimulation by 3,3′,5-triiodothyro-acetic acid (Triac)1. Furthermore, a deiodinase has been characterized in amphioxus, which is inactive towards iodothyronines but effectively deiodinates Triac2. Together, these findings suggest that Triac is the active TH in amphioxus. Early studies of the metabolism of T3 in humans and animals have indicated the formation of Triac but the exact nature of this process has not been established3. The first step in the conversion of T3 to Triac is likely catalyzed by one or more aminotransferases, resulting in the formation of 3,3′,5-triiodothyropyruvic acid. The latter may then be oxidized to Triac, but it is unclear what enzyme, if any, is involved in this oxidation. Recent studies in our lab have resulted in better insights in the pathway by which T3 is converted to Triac. Triac has been used for TSH-suppressive therapy in patients with thyroid cancer or patients with thyroid hormone resistance, based on a greater central than peripheral activity of Triac. It is now also tested as a therapy for patients with severe X-linked psychomotor retardation (Allan-Herndon-Dudley syndrome, AHDS) caused by mutations in the TH transporter MCT8. MCT8 is essential for TH transport into and inside the brain, and TH deficiency in the developing brain results in severe neurological deficits. Supported by *in vitro* and animal experiments, Triac does not require functional MCT8 for transport into brain cells, and would thus be effective in restoring thyromimetic activity in the brain of AHDS patients3.
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S7.2

Tetrac as an antiangiogenic agent in cancer
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In 2005, Bergh *et al*. first described a cell surface receptor for thyroid hormones (TH) T3 and T4 on integrin αvβ3 that is expressed on tumour cells and dividing endothelial cells. The deaminated T4 derivative tetraiodothyroacetic acid (tetrac) is a specific inhibitor of integrin-mediated TH action. Building on Paul Davis' pioneer studies, we are investigating the effects of TH and tetrac on mesenchymal stem cells (MSCs), important progenitor cells of the tumour's fibrovascular network, in the context of tumour angiogenesis. We were the first to show that recruitment and invasion of MSCs into tumours is significantly enhanced by TH stimulation and blocked by tetrac. In addition, we demonstrated that tetrac reverses the differentiation of MSCs towards a cancer-associated fibroblast-like and pro-angiogenic phenotype that occurs under tumour cell-conditioned medium and TH stimulation. Moreover, tetrac inhibited TH-stimulated endothelial cell tube formation, as did supernatant from MSCs stimulated with tumour cell-conditioned medium and TH in the presence of tetrac. Further, we established a reporter gene system by transfecting MSCs with the sodium iodide symporter (NIS) under control of the promoter for the vascular endothelial growth factor (VEGF), a critical angiogenesis mediator, leading to enhanced NIS-mediated iodide uptake activity after stimulation with tumour cell-conditioned medium and TH that was blocked by tetrac. In an orthotopic hepatocellular carcinoma xenograft mouse model, tumoural radioiodide uptake, measured by iodide-124 PET, demonstrated successful tumoural recruitment of MSCs followed by VEGF promoter-driven NIS expression. In hyperthyroid animals, tumoural radioiodide uptake was strongly enhanced compared to euthyroid and hypothyroid mice, while treatment with tetrac markedly reduced uptake, confirming inhibition of TH-mediated stimulation of VEGF by tetrac. Our data suggest that tetrac blocks the pro-angiogenic signalling of TH in MSCs via integrin αvβ3, providing further evidence of the anti-angiogenic activity of tetrac in the context of tumour stroma formation.
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S7.3

Thyroid hormones, metabolites, and analogs: Potential therapies for non-alcoholic fatty liver disease and other metabolic conditions
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Singapore.

Thyroid hormones (THs) are known to regulate both lipid, glucose, and cholesterol metabolism. These effects have led to biochemical and molecular studies on the roles that they and their metabolites have on these processes. Additionally, TH analogs have been developed to improve metabolic conditions such as hypertriglyceridemia hypercholesterolemia, and obesity while minimizing side effects such as tachycardia and osteoporosis that occur in hyperthyroidism. Typically, these analogs have preferential binding to the TH receptor beta isoform or preferential uptake by the liver. It now has been appreciated that THs also may have beneficial effects for the treatment of non-alcoholic fatty liver disease (NAFLD). We and others observed that TH and TH analogs decreased hepatosteatosis in animal and cell culture models of NAFLD by stimulating autophagy and b-oxidation of fatty acids. Additionally, we found that intrahepatic triiodothyronine (T3) levels were decreased and serum T3 levels were normal in an animal model of NAFLD. These findings suggested that there may be 'liver-specific hypothyroidism' in NAFLD so serum TH levels alone may not be sufficient to determine the TH status within the liver in this condition. We also have shown that the TH metabolite, diiodothyronine (T2), decreased hepatosteatosis in rats fed high fat diet by stimulating autophagy and acylcarnitine flux. We recently completed a pilot clinical study showing that low dose levothyroxine supplementation was able to decrease hepatosteatosis in euthyroid adult Asian men with diabetes. Taken together, these findings suggest that TH supplementation or the employment of TH metabolites and analogs may have therapeutic promise for the treatment of NAFLD and other metabolic conditions.
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Bone fragility – from bench to clinic

S8.1

Clinical spectrum of new monogenic forms of osteoporosis

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Genetic factors play an important role in osteoporosis. Several monogenic forms of osteoporosis have been recognized. The most common of these is osteogenesis imperfecta (OI) in which dominantly inherited mutations in the genes encoding type I collagen (COL1A1 and COL1A2) are responsible for approximately 90% of the cases. Several rare autosomal recessive forms of OI have also been described. In these the defects lie in proteins involved in posttranslational modification of type I collagen. Recent discoveries have further elucidated the genetic determinants of early-onset skeletal fragility and several forms not related to type I collagen have been identified. The discovery of LRP5 mutations in osteoporosis-pseudoglioma syndrome and in early-onset osteoporosis first indicated that the WNT signaling pathway plays an important role in bone mass accrual. Several other studies thereafter, including our discovery of WNT1 mutations in early-onset osteoporosis, have further highlighted the pathway's significance in various disorders of low and high bone mass and provide evidence for the potential of WNT targeted therapies in osteoporosis treatment. The X-chromosomal osteoporosis caused by PLS3 gene mutations is another example of novel monogenic forms of osteoporosis that can be used to study cellular mechanisms leading to bone fragility. PLS3 osteoporosis affects mainly males and leads to severe progressive spinal osteoporosis; even females carrying the mutation may develop symptomatic osteoporosis. Our studies in patients with PLS3 deletions suggest that PLS3 plays a significant role in bone mineralization but the pathogenetic mechanisms are not fully understood. Several other monogenic forms of osteoporosis are under investigation. These highlight the complexity of molecular mechanisms governing normal

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S8.2

Abstract unavailable.

S8.3

Hypophosphatasia – diagnosis and treatment

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Hypophosphatasia (HPP) is a rare inborn metabolic disorder due to ALPL gene (1p36.12) mutations leading to deficient activity of the Tissue Non-Specific Alkaline Phosphatase (TNSALP), a homodimeric cell surface phosphohydrolase expressed in multiple tissues. Autosomal recessive or dominant inheritance of more than 300 different loss-of-function mutations cause accumulation of TNSALP substrates, including inorganic pyrophosphate (PPi), a potent inhibitor of mineralization, Pyridoxal 5-phosphate, the major circulating form of Vitamin B6 and Phosphoethanolamine (PEA). The clinical spectrum of disease manifestations both in terms of severity and organ involvement is remarkably broad, ranging from stillbirth and perinatal/infantile life-threatening symptoms, including chest and lung hypoplasia and pyridoxine-dependent seizures over premature loss of deciduous teeth and rachitic bone deformities in early childhood to unspecific musculoskeletal issues with rheumatoid/inflammatory pain, muscular weakness and fatigue along with compromised physical performance and recurrent, sometimes poorly healing fractures and bone marrow lesions. Beyond assessment family and individual medical history and clinical examination, diagnostic workup includes laboratory evaluation with Alkaline Phosphatase activity below age/sex adjusted normal range, elevated substrate levels (PLP in serum/plasma and urinary PEA) and eventually genetic testing for ALPL-Gene mutations, even though is to be considered that available evidence does not support the idea of a reproducible or meaningful genotype-phenotype correlation. Treatment is always multidisciplinary, including different medical specialties depending on prevailing organ manifestations and has to be tailored to individual needs. Following multinational approval of Asfotase alfa, a recombinant bone anchoring human alkaline phosphatase, enzyme replacement therapy (ERT) is available in Europe to treat bone manifestations of the disease in patients with childhood onset HPP. Study data on ERT clearly shows significantly improved survival of treated children as compared to a historical cohort. Further treatment modalities in addition and for less severely affected patients include analgesic medication with NSAIDs, supportive care with physiotherapy and phosphate reduced diet or phosphate binders and interventions to improve bone health including moderate Vitamin D supplementation and osteoanabolic treatment on an individual per-case decision, while avoiding bisphosphonates which appear to aggravate HPP-associated bone manifestation.

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EAA /ESE Session: Male gonadal function versus general health and vice versa

S9.1

Abstract unavailable.

S9.2

Klinefelter syndrome – a challenge for endocrinologists

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Klinefelter syndrome (KS) is usually perceived as a disorder causing infertility and androgen deficiency and indeed, KS is the most frequent form of hypogonadism with 1 – 2 cases per 1,000 males and with a 47,XXY karyotype, the most frequent male chromosome disorder. Yet the incidence of the syndrome is probably significantly higher than the diagnosed casas suggest. Although subtle symptoms may be already evident in childhood and puberty, androgen deficiency usually only becomes evident in early adulthood. The manifold comorbidities of the KS should provide clues to the underlying genetic disorder. In the young patient neurological and psychological deficits may become evident e.g. in verbalization and attention, with learning difficulties resulting in professional and socio-economic underachievement. At a later age metabolic disturbances may occur (metabolic syndrome, diabetes type 2, venous thromboembolism, cardiovascular diseases, osteoporosis and fractures, autoimmune diseases, mediastinal tumors and mammary carcinoma). Doctors and hospitals consulted for these comorbidities often fail to recognize the underlying condition. However, the most prominent somatic feature of KS, the very small testes, are not investigated routinely so that this clue to the karyotype as the decisive diagnostic procedure remains overlooked. Although testosterone substitution is usually prescribed when testosterone serum levels become subnormal, optimal modalities and onset of treatment have not been explored by controlled trials. Similarly, although paternity has become possible by TESE and ICSI, the optimal time for testicular biopsy and the possible benefit of any pretreatment remain unclear. Although psychological support has beneficial effects especially in the transition phase, it is only provided in selected centers. Further elucidation of the genetic basis underlying the wide phenotypical heterogeneity in KS should provide new diagnostic and therapeutic approaches, e.g. paternal or maternal origin of the supernumerary X-chromosome, undetected mosaicism, extent of X-chromosome inactivation and polymorphism of the androgen receptor. To coordinate these approaches and to initiate the required research remains a challenge to the endocrinologists.

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S9.3

Does 'healthy obesity' exist in andrology?

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Introduction
Obesity is a cause of erectile dysfunction (ED) whereas its relationship with male infertility is more conflicting. The term metabolically healthy obesity (HO) has been used to describe an obese phenotype that does not have the burden of any metabolic disorder. The aim of the present study is to analyse the contribution of HO in the pathogenesis of ED and male infertility and to verify the value of HO in predicting major adverse cardiovascular events (MACE).
Methods
An unselected series of 4382 (51.4 ± 13.1 years) men with sexual dysfunction (SD) and 222 (37.3 ± 8.6 years) males of infertile couples were studied. A subset of men with SD ($n = 1687$) was enrolled in a longitudinal study. Several clinical, biochemical and ultrasound parameters were evaluated. HO was defined as the presence of body mass index > 30 kg/m2, HDL > 40 mg/dl and absence of diabetes or hypertension.
Results
Among the patients with SD, 723 (16.5%) were obese and among them 163 (3.7%) were HO and 560 (12.8%) had a complicated obesity (CO). Similarly, among men of infertile couple 55 (24.8%) were obese and among them 18 (8.1%) had HO and 37 (16.7%) CO. After adjustment for confounders, when compared to healthy normal weight individuals, in both samples, either subjects with HO or CO had lower total T levels. Conversely, no difference between HO and CO were observed. In addition, in both samples men with CO but not those with HO reported worse erectile function when compared to healthy normal weight individuals. When PCDU parameters were considered, peak systolic velocity evaluated in flaccid conditions was lower in both HO and CO when compared to normal weight subjects in subjects with sexual dysfunction as well as in those of infertile couples. In addition, men of infertile couples with CO but not those with HO showed higher risk of ultrasound and biochemical (semen IL-8) features of prostatic inflammation when compared to normal weight subjects. Conversely, no differences in seminal parameters among groups were observed. Finally, the longitudinal study, after adjusting for confounders, both HO and CO were independently associated with a higher incidence of MACE (HR = 4.800 [1.265;18.214]; HR = 3.041 [1.078;8.573] 2.469 [1.019;5.981], respectively; both $P < 0.05$), when compared to the rest of the sample.
Conclusions
Our data suggest that healthy obesity induces subclinical ED and prostatic inflammation independent of T levels and it is associated with an increased CV risk.

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Hot topics in NETs

S10.1

Whole genome landscape in pancreatic neuroendocrine tumours

Vincenzo Corbo
Italy.

Pancreatic NETs (PanNETs) are characterized by recurrent molecular alterations, including genetic inactivation of MEN1, ATRX/DAXX, and activation of the PI3K/mTOR pathway. The International Cancer Genome Consortium effort on PanNETs provide a first snapshot of how heterogeneous is the combination of genetic alterations that drive this tumour type, yet converging into four pathways whose alteration has been enriched by newly discovered mechanisms. Whole-genome sequencing of 102 primary PanNETs and validation on additional 62 cases defined the genomic events that characterize their pathogenesis. The mutational signatures PanNET harbour include a deficiency in G:C > T:A base excision repair due to inactivation of MUTYH, which encodes a DNA glycosylase involved in base-excision repair. Clinically sporadic PanNETs contain a larger-than-expected proportion of germline mutations, including previously unreported mutations in the DNA repair genes MUTYH, CHEK2 and BRCA2. Together with mutations in MEN1 and VHL, these mutations occur in 17% of patients. Somatic mutations, including point mutations and gene fusions, are commonly found in genes involved in four main pathways: chromatin remodelling, DNA damage repair, activation of mTOR signalling (including previously undescribed EWSR1 gene fusions), and telomere maintenance. In addition, gene expression analyses identified a subgroup of tumours associated with hypoxia and HIF signalling. While calling for further integration of genetic and epigenetic analyses, these data allow reconciling previous findings in a defined frame, and may provide clinical research with markers for patients stratification and to guide targeted therapy decisions.

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S10.2

Abstract unavailable.

S10.3

Treatment update on carcinoid syndrome and carcinoid heart disease

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Abstract unavailable.

Novel aspects of Craniopharyngioma

S11.1

Molecular pathogenensis of craniopharyngioma

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Craniopharyngiomas (CPs) are tumours located in the sellar and parasellar region, thought to have an embryonic origin and/or to arise from pituitary progenitors/stem cells. They have an overall incidence of 1–2 new cases/million population/per year and are subdivided into two histologically different subtypes, adamantinomatous (aCPs) and papillary (pCPs). The clinical manifestations at diagnosis for CPs are: headache, visual disturbances, polyuria/polydipsia, endocrine dysfunction such as growth retardation, puberty disturbances and obesity. The current therapy of choice is complete resection or partial resection with the intention to maintain optic nerve and hypothalamic functions if these areas are affected. Overall surgical survival rates are high (90%), although post-surgical morbidity is present in 100% of the patients, leading endocrine deficiencies and lifelong treatment. Recently, molecular studies have identified that the two CPs subtypes are genetically distinct with aCPs mainly harboring mutations in Wnt signaling effector, β-catenin, and pCPs in the BRAFV600E oncogene. These molecular findings have led to the identification of possible therapeutic treatments for pCPs using BRAF inhibitors, which highlights the importance genetic studies for the identification of future targeted therapies. Transgenic murine models of aCPs have revealed novel therapeutic targets that could be beneficial for aCP treatments and identified pathways important in tumour progression both in humans and murine models. Moreover, we present genetic studies from a large cohort of aCP patients that suggests that the reported mutual genetic exclusivity of CPs subtypes, is in fact more heterogeneously complex than previously thought, and that the underlying genetic drivers for a large proportion of CPs patients remains unknown.

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S11.2

Bariatric surgery as treatment in craniopharyngioma

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Patients with craniopharyngioma suffer from excess mortality and morbidity, especially patients with childhood onset of the disease. The impaired outcome in

these patients is in part related to hypothalamic obesity, which is mainly caused by hypothalamic damage. The hypothalamic damage seems to result in autonomic nervous system dysfunction as well as leptin and insulin resistance. These factors negatively affect food intake, food satisfaction, metabolism and energy expenditure. In 'common' obesity, bariatric surgery has been shown to be highly effective. Therefore, bariatric surgery has been proposed as a therapeutic option in patients with craniopharyngioma and hypothalamic obesity. Multiple aspects need to be considered in obese patients with craniopharyngioma. For example, will bariatric surgery in patients with hypothalamic obesity lead to similar results to those found in patients with 'common' obesity and, also, will the surgery and/or the weight loss have a significant effect on hormonal replacement therapy? The talk will review the effects of bariatric surgery in patients with craniopharyngioma. Furthermore, the results of the latest collaborative study, between Erasmus University and Gothenburg University will be presented. In this study, eight patients with craniopharyngioma received bariatric surgery and was compared to closely matched patients receiving the same type of surgery for 'common' obesity. The craniopharyngioma patients were followed for 2 years regarding effects on body weight, hormonal replacement therapy and side effects.

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S11.3

The psychosocial, neuroendocrine and cognitive effects of childhood craniopharyngioma

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UK.

Craniopharyngiomas are paradoxically considered 'benign' and hence curable by complete excision. Despite a high survival rate, however, this notion belies a high morbidity and propensity for premature mortality from neuroendocrine disease and treatment complications in those diagnosed in childhood, whose disease differs from that in adulthood. These result from a proximity to, and invasion of, vital ophthalmic, neurometabolic, neurocognitive and neuroendocrine pathways, and the subsequent impact on normal growth, learning and maturation processes in the developing child. Some of these are life threatening, and all are life changing. The devastating effects of hypothalamic injury are poorly understood, whilst endocrine replacement therapy and neurocognitive rehabilitation are not always timely or streamlined into treatment pathways. In 2005, the first UK consensus management guidelines recognised the surgical contribution to hypothalamic injury and advocated conservative debulking strategies and up front radiation to stabilise disease, avoiding further surgical hypothalamic harm or that due to recurrence. Poor cognitive and endocrine outcomes have traditionally been blamed on cranial radiation rather than pre-existing disease (eg.diagnostic delays, recurrence) or treatment (eg.radical excision) variables, with increasing attempts to avoid or refine this in children. Since 2009, the theoretical cognitive advantages afforded by the reduced penumbral scatter of proton beam irradiation has made this the NHS UK standard of care, patients being sent to USA for therapy, without a risk-benefit analysis as compared with photons.We will present neuroendocrine and cognitive outcome data on our cohort of 54 patients treated on a conservative surgical and early radiation strategy over two decades, and compare these with our own historical, radical surgery series (published 1996) by treatment era, and with other published series. Our early longitudinal evidence suggests tumour position, size, recurrence and Paris grade of hypothalamic involvement at diagnosis, as well as the surgical and radiation strategy (early vs late) are greater influencers of outcome than type of radiation (protons vs photons), and a 2-staged surgical and early radiation strategy which stabilises disease, can reduce the neuroendocrine morbidity burden. Infants and children under 3 years at diagnosis are particularly vulnerable to poor outcomes, with greater prevalence of blindness at presentation, diagnostic delays, stroke, recurrent cystic tumours treated with experimental intracystic interferon, and avoidance of radiaition considered too neurotoxic. A considered 2-stage surgical strategy avoiding hypothalamic harm, timely radiation and intensive interval neuroendocrine / cognitive assessment and rehabilitation, are more likely to improve outcomes than radiation type.

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Why do fractures occur in endocrine disorders, and how should they be handled?

S12.1

Abstract unavailable.

S12.2

Bone quality evaluation in Pituitary diseases

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The skeleton consists of cortical bone and trabecular (cancellous) bone. Cortical bone, which comprises 80% of the skeleton, is designed to provide rigidly and strength and is predominantly found in the long bones, e.g. at the femur. Cancellous bone has a more flexible design with interconnecting trabecles, and is metabolically more active then cortical bone. The balance between formation and resorption is essential for maintaining a normal bone mass and skeletal integrity. Disruptions in the ratio of bone formation and resorption in favour of resorption will ultimately lead to progressive bone loss and increased bone fragility. In daily clinical practice, Bone Mineral Density (BMD) measurements using DXA remain the corner stone for the diagnosis of osteoporosis. BMD has been shown to be a strong predictor for fractures however there is increasing evidence that factors other than BMD determine bone fragility and thus fracture risk. These underlying secondary risk factors for fractures should be taken into account in the assessment of an individual's fracture risk and are usually present in patients with pituitary diseases. These secondary factors may be identified by medical history and evaluated and confirmed using appropriate laboratory investigations including thyroid, gonadal function. But Cushings disease, Acromegaly or growth hormone deficiency should be considered as well. Besides laboratory examinations, additional radiological evaluation should take place when evaluating these patients. The presence of one or more vertebral fractures has been shown to represent a strong independent predictor for future vertebral and for non-vertebral fractures. Vertebral fractures have been shown to be associated with increased morbidity and mortality. Increased incidence of Vertebral fractures have been reported in patients with Acromegaly and Growth Hormone deficiency where bone mass might even be within the normal range. Therefore other techniques should also be explored to further evaluate fracture risk in patients with pituitary diseases.

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S12.3

Parathyroid dysfunctions – bone mass and fractures in primary hyperparathyroidism

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Norway.

Primary Hyperparathyroidism (PHPT) is the most common disease among parathyroid disorders compared to Chronic Hypoparathyroidism, Calcium Sensor disorders (loss or gain of function mutations) or Parathyroid Cancer. The clinical presentation of PHPT has changed dramatically after the increased accessibility to biochemical analyses. The diagnosis is today often made by change in patients without specific symptoms. Operative treatment is always an option and recommended in patient with markedly increased calcium levels or typical symptoms. Bone metabolism in PHPT has been systematically investigated. Bone turnover is increased with a reversible bone loss at the trabecular surface, whereas there seems to be a non-reversible loss at the cortical level. Epidemiological and observational studies have demonstrated increased fracture rate in PHPT, and long term longitudinal studies have revealed a significant bone loss primarily at cortical sites with observation. Thus, diagnostic osteoporosis by DXA or low energy fractures is regarded as treatment indication (operation) even in the mildest cases. The primary treatment of PHPT is surgical removal of the enlarged parathyroid mass, most often being a parathyroid adenoma. Surgery (or anti-resorptive, medical treatment) will decrease bone turnover, filling the enlarged remodeling space and thereby in theory normalize fracture rate. However, only few prospective studies have looked into the benefit of operation versus

conservative observation without intervention in PHPT. Observational data and recent prospective, randomized studies indicate that bone mass might become critical low with prolonged observation. In alignment, there seems to be a treatment effect on fracture rate with surgical treatment. Most patients with PHPT will present with few if any symptoms, high normal or slightly increased calcium levels with only moderately elevated PTH. Differential diagnoses must be ruled out and familiar or syndromic forms identified. An increased awareness on bone mass and fracture rate in patients to be followed without intervention is recommended.

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The colours of fat

S13.1

Brown adipose tissue as an endocrine organ

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Spain.

Brown adipose tissue (BAT), in addition to its role in adaptive thermogenesis, secretes regulatory factors (brown adipokines or 'batokines') that have autocrine, paracrine, and endocrine actions. Local secretion of brown adipokines by brown adipocytes target distinct cell types in the tissue (e.g. vascular cells, sympathetic nerve endings, immune cells) and promote the remodeling of BAT in response to distinct physiological conditions requiring adaptive thermogenesis. Evidence from BAT transplantation in rodents led to hypothesize that brown adipokines may have endocrine actions which may be involved in the systemic healthy effects (mainly prevention of insulin resistance and obesity) of active brown fat. There is evidence that such healthy effects occur also for the human brown adipocyte secretome. Brown adipokines identified to date are polypeptides, lipid molecules or microRNAs. However, a comprehensive knowledge of the secretome from BAT fat is still lacking. The identification and characterization of brown adipokines may help to identify novel tools for treatment of metabolic diseases, due to the expected healthy properties of signaling molecules released by BAT. Moreover, circulating biomarkers of BAT activity are not available at present, and research on brown adipokines may contribute to the identification of such systemic biomarkers that will be particularly useful in clinical research. Recently, a distinct type of adipose tissue has been identified, the so-called 'beige' adipose tissue which contain thermogenic 'beige' adipocytes resembling brown adipocytes. Several experimental data suggest that the extent of induction of 'beige' adipose tissue in response to thermogenic challenges is associated with protection against obesity and hyperglycemia. To date, the secretome of 'beige' adipocytes appears to resemble that from brown adipocytes, but research for potential differential secretion beige-versus-brown adipokines is ongoing.

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S13.2

Adipose tissue browning in mice and men

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Austria.

Promotion of brown adipose tissue (BAT) activity or browning of white adipose tissue has shown great potential as anti-obesity strategy in numerous preclinical models. The discovery of active BAT in humans and the recent advances in the understanding of human BAT biology and function have sparked this field of research. Pharmacological stimulation of energy expenditure to counteract obesity has always been an intriguing therapeutic concept; the identification of the specific molecular pathways of brown fat function is an important step towards developing novel agents that harness the termogenic potential of adipocytes. Two distinct strategies are currently being pursued; one is the activation of bone fide BAT, the other is the induction of BAT-like cells or beige adipocytes within white fat depots, a process called browning. Recent evidence suggests that both phenomena can occur in humans. Cold-induced promotion of BAT activity is strongly associated with enhanced thermogenesis and energy expenditure in humans and has positive effects on fat mass and glucose metabolism. Despite these encouraging results, a number of issues deserve additional attention including the distinct characteristics of human versus rodent BAT, the heterogeneity of human BAT depots, or the identification of the adipocyte precursors that can give rise to thermogenic cells in human adipose tissue. In addition, many exogenous and endogenous factors have been identified to regulate a browning program in human and mouse adipocytes. This talk summarizes the cellular and molecular mechanisms of adipocyte browning, its functional relevance for energy metabolism and the therapeutic potential for obesity.

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S13.3

Browning of adipose tissue in humans

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Finland.

In 2009 three independent research groups confirmed the existence of metabolically active brown adipose tissue in human adults. There is increasing evidence that enhanced BAT function can improve systemic health in humans by utilizing glucose and lipids from the circulation and by increasing metabolic rate. Therefore BAT activation could provide a strategy to combat the increasing epidemic of obesity and type 2 diabetes. The function of BAT is controlled by various endogenous factors, and hormones including the thyroid hormones. In states of disease or abnormal metabolism, such as hyperthyroidism or obesity, the regulatory systems may become impaired. Positron emission tomography (PET) has provided a non-invasive way to investigate BAT function in humans in vivo. BAT glucose uptake increases in lean men up to 10-fold during cold exposure. The potential of this imaging technique has only partly utilized and focused on glucose metabolism only. Although there is growing amount of reports on BAT activation in humans, evidence regarding the browning of WAT is limited. We and others have shown that BAT activity in morbidly obesity increases after bariatric surgery. Chronic cold exposure for 6 weeks at 17°C during 2-hour per day resulted increase in BAT activity and cold-induced thermogenesis in on-obese individuals with low BAT activity in a study of Yoneshiro et al. The stimulation of BAT during the cold is mediated via NE-dependent pathway. Mirabegron, a beta3-adrenergic receptor agonist used for the treatment of overactive bladder was promising in humans in a short but not in a longer intervention. Irisin is one of the promising ones release e.g. by exercise. The fibroblast growth factor-21 (FGF-21) also interacts with the FGF receptors on the brown adipocytes and they have been shown to stimulate glucose oxidation and thermogenic mechanism in the BAT. Studies about effects of exercise to induce browning have given controversial results. This might be partly due altered substrate metabolism towards utilization of more fatty acids, which is more difficult to measure directly in human BAT. Even the changes in outdoor temperature seems to be blunt the exercise induced effects. The physiological role of BAT in adult humans is still largely open. Totally new areas are coming up constantly. Recent studies have suggested a link between BAT volume and total and spine bone mineral density mainly in women. Numerous efforts are ongoing to find drugs for browning. The heat is still on.

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Neuroendocrine basis of reproductive disorders

S14.1

Developmental wiring of GnRH neurons

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Puberty is a transition period of reproductive development from juvenile stages to adulthood and depends upon activity of gonadotropin-releasing hormone (GnRH) neurons. GnRH neurons are initially activated in utero, but remain quiescent throughout the juvenile period. Premature reactivation of GnRH neurons results in precocious puberty in mice and humans, but the mechanisms underlying developmental control of GnRH neuron activity remain unknown. The neuropeptide kisspeptin, a potent activator of GnRH neurons that is implicated as a critical permissive signal triggering puberty and a major regulator of the adult female hypothalamus-pituitary-gonadal (hpg) axis, is paradoxically produced by neurons in the developing brain well before puberty onset. We have delineated the underlying neural circuitry using conditional genetic transsynaptic tracing in female mouse embryos. We find that kisspeptin-producing neurons in the arcuate nucleus (ARC) already communicate with a specific subset of GnRH neurons in utero. We show that ARC kisspeptin neurons are upstream of GnRH neurons and that GnRH neuron connectivity to ARC kisspeptin neurons does not depend on their spatial position in the brain. Furthermore, we demonstrate that the neural circuits between ARC kisspeptin and GnRH neurons are fully established and operative before birth. Most GnRH neurons express the kisspeptin receptor GPR54 upon circuit formation, suggesting that the signaling system implicated in gatekeeping puberty becomes operative in the embryo. Distinct roles have been

proposed for AVPV and ARC kisspeptin neurons during reproductive maturation and in mediating estrogen feedback on the hpg axis in adult females. However, little is known about kisspeptin neuron connectivity in adult female mice. We analyzed the connectivity of individual kisspeptin neurons with the GnRH neuron population in adult female mice with a single cell resolution. Only subsets of AVPV and ARC kisspeptin neurons are synaptically connected with GnRH neurons demonstrating functional specialization within the two kisspeptin neuron populations.

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S14.2

Neuroendocrinology right from the nose: Genetics and pathophysiology of the olfacto-genital syndrome (Kallmann syndrome)

Jean-Pierre Hardelin
France.

Kallmann syndrome is a developmental disorder that associates anosmia, related to olfactory bulb aplasia, with congenital hypogonadotropic hypogonadism caused by GnRH deficiency, clinically characterized by the absence of spontaneous puberty and infertility. GnRH deficiency results from the incomplete embryonic migration of neuroendocrine GnRH-cells from the nasal epithelium to the hypothalamic region of the brain, as a consequence of the premature interruption of olfactory, vomeronasal and terminal nerve fibres, which normally guide these cells during their migration to the brain. This developmental connection between the central control of reproductive organs and the peripheral olfactory system (both affected in Kallmann syndrome) accounts for the aforementioned olfacto-genital pathological sequence. Kallmann syndrome can be isolated or associated with various non-reproductive non-olfactory additional anomalies, depending on the causal genes. Kallmann syndrome is genetically heterogeneous, with several different modes of transmission: X chromosome-linked recessive, autosomal dominant, autosomal recessive, and presumably oligogenic. The best characterized causal genes include ANOS1 (anosmin 1), FGFR1 (fibroblast growth factor receptor 1, also involved in Hartsfield syndrome), FGF8 (fibroblast growth factor 8), PROKR2 (prokineticin receptor 2), PROK2 (prokineticin 2), FEZF1 (FEZ family zinc finger 1), SOX10 (sex determining region Y-box 10, also involved in Waardenburg syndrome), and CHD7 (chromodomain helicase DNA-binding protein 7, also involved in the CHARGE association). Notably, this list implicates at least two different cell signalling systems (i.e., signallings by FGFs and by prokineticins) in Kallmann syndrome molecular pathogenesis. However, mutations in any of these genes are found in less than 50% of the patients, indicating that other disease genes remain to be discovered. The complex genetics of Kallmann syndrome, including a biased sex ratio (predominance of affected males) and monogenic versus oligogenic modes of transmission, will be discussed.

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S14.3

Abstract unavailable.

EYES: New aspects in the study of neuroendocrine diseases

S15.1

Introduction to EYES

Tatjana Isailovic
Serbia.

The ‘European Young Endocrine Scientists’ (EYES) founded in 2011, is a committee under the patronage of the European Society of Endocrinology (ESE). The primary goal of this committee is to increase the mutual exchange of ideas and knowledge between early career endocrinologists across Europe, in both basic and clinical research. EYES enables young endocrinologists 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. The committee provides a platform for young scientists in endocrinology to make them feel welcome at ESE and to familiarize with the society’s conferences. EYES aims to support annual meetings exclusively for young scientists in different European countries (The Netherlands, Serbia, Italy, Portugal, Russia and Poland in 2018), giving 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 web page and Facebook page, visit us at EYES symposium and join our social evening event during ECE 2018.

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S15.2

Abstract unavailable.

S15.3

Epigenetic and metabolic reprogramming of SDH deficient pheochromocytomas and paragangliomas

Judith Favier
France.

SDHA, B, C, and D (SDHx) genes encode the four subunits of succinate dehydrogenase (SDH), a mitochondrial enzyme of the tricarboxylic acid (TCA) cycle that oxidizes succinate into fumarate. They were the first genes encoding a mitochondrial enzyme demonstrated to act as tumor suppressors, an important finding supporting the hypothesis of a direct link between mitochondrial dysfunction and cancer proposed by Otto Warburg in the 1920’s. It is estimated that germline mutations in SDHx genes represent around half of inherited pheochromocytoma and paraganglioma (PPGL), which are referred to as Cluster 1 tumors. In PPGL, SDH loss-of-function results in the accumulation of succinate, which acts as an oncometabolite, by inhibiting 2-oxoglutarate-dependent dioxygenases among which HIF prolyl-hydroxylases drive a pseudohypoxic response and promote angiogenesis and DNA demethylases cause a hypermethylator phenotype. This presentation will show how our team uses genetic and OMICs analyses on the large series of human PPGL gathered by the French COMETE network, combined with experimental studies on Sdhb knockout cells and xenografts to decipher these mechanisms and develop tools to evaluate the response to anti-angiogenic or demethylating therapies. It will also show how we used OMICS analyses combined with whole-exome sequencing to identify new PPGL susceptibility genes within the cluster 1 group of PPGL. Using such an approach, we previously identified the first PPGL case harboring a germline FH gene mutation and now discovered a new mitochondrial tumor suppressor gene encoding an unsuspected carrier. These finding demonstrate the central role of mitochondrial deficiencies in the predisposition to paragangliomas.

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S15.4

Abstract unavailable.

S15.5

Abstract unavailable

S15.6

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Changing practice in the management of thyroid neoplasms

S16.1

New steps in the genomic alterations of thyroid malignancies

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Spain.

Thyroid cancer is the most common endocrine malignancy giving rise to one of the most indolent solid cancers, but also one of the most lethal. In recent years, systematic studies of the cancer genome, most importantly those derived from The Cancer Genome Altas (TCGA), have catalogued aberrations in the DNA, chromatin, and RNA of the genomes of thousands of tumors relative to matched normal cellular genomes and have analyzed their epigenetic and protein consequences. One unexpected observation is that the genome is massively transcribed in non-coding RNA which role is now beginning to be understood. We now know that the alteration of the transcriptome is not restricted to the production of aberrant levels of protein-coding RNAs (less than 2% of the genome) but also refers to the aberrant expression of multiple noncoding members that comprise the human genome, being microRNAs the most studied and, more recently, long non-coding RNAs (lncRNAs). Moreover, the interplay between lncRNAs and microRNAs appears to be a new level of regulation of importance in several malignancies. Cancer genomics is therefore providing new information on cancer development and behavior, as well as new insights into genetic alterations and molecular pathways. From this genomic perspective, we will review the main advances concerning some essential aspects of the molecular pathogenesis of thyroid cancer focusing on the increasing role of non-coding RNAs. This look across these genomic and cellular alterations results in the reshaping of the multistep model of thyroid tumors development and offers new tools and opportunities for further research and clinical development of novel treatment strategies.

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S16.2

Composite approach in the evaluation and management of thyroid nodule

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Thyroid nodules are common in the population. Ultrasound would detect nodules, in about 25% of the adult and half of the elderly population(>60 years). Only 5% of these nodules are malignant, and 60–70% of the detected benign nodules, remains similar or decrease in size during the long term follow-up. Few nodules, i.e >1.3 cm, would function autonomously and cause thyrotoxicosis. Rarely, large single nodules or multinodulated glands could cause compressive symptoms, or esthetic problems. Thus the clinician should plan to treat a small subgroup of patients carrying either of the problems described above and could simply follow-up the majority of the patients without any intervention. Ultrasound is the main tool, which physicians themselves, should use for picking up the high risk cases and decide FNAB. After the initial definition of TIRADS by Horvath et al, other thyroid organizations (ATA, AACE/AME) and recently ETA, developed standardized US risk stratification systems for reporting US features. Aim is to reliably define US assessment categories that can be used to communicate the expected risk of thyroid cancer and define those to be referred for FNAB. After the initial evaluation, appropriate surgical or medical interventions should be undertaken if needed. İ.e.; Surgery for the malignant nodules and/or large compressing multinodulated glands. Percutaneous ethanol injection (PEI) for large cystic nodules. Radiofrequency, percuteneous laser ablation (RFA, PLA) or high intensity focused ultrasound (HIFU) for single or limited number of nodule(s) causing esthetic or compressive problems. Radioiodine for autonomously functioning nodules in benign glands. Majority of the nodules would require no management, and it is the physicians responsibility to avoid unwarranted surgical or invasive intervention. Thyroidectomy is still, frequently, unnecessarily performed, and 30–40% of the postsurgical hypothyroid patients is either under or over replaced.

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S16.3

Abstract unavailable

Recent advances in Primary Adrenal Macronodular Hyperplasia

S17.1

Adrenal development and benign tumor formation

Pierre VAL
France.

The adrenal cortex arises from the adrenogonadal primordium, which is also involved in the formation of the gonadal anlagen and is characterized by expression of the nuclear receptor Sf1. After individualisation, the adrenal primordium undergoes a series of developmental events that culminate with establishment of functional zonation, characterised by differentiation of zona glomerulosa and zona fasciculata. In the past 7 years, we have developed a number of mouse models recapitulating alterations of WNT/b-catenin and PKA signalling pathways identified in patients presenting with adrenal cortex tumours. This has allowed us to demonstrate that constitutive WNT/b-catenin pathway activation causes the development of both benign aldosterone producing adenomas and to a lesser extent adrenal cortex carcinomas, whereas constitutive PKA signalling is associated with the development of benign glucocorticoid-producing tumours. Beyond tumourigenesis, these experiments have also shed light on the mechanisms involved in adrenal cortex development and in particular functional adrenal cortex zonation. Indeed, we have shown that this process relies on a subtle equilibrium between WNT pathway activation by WNT4/RSPO3 in zona glomerulosa and PKA activation by ACTH/MC2R in zona fasciculata. These data emphasize the idea that adrenal tumourigenesis and differentiation share common regulators and pathways. This is further exemplified by our latest experiments showing that the histone methyltransferase EZH2, which is overexpressed in adrenal cortex carcinomas, is also a key player in regulating steroidogenic cell differentiation and maintaining adrenal identity as opposed to gonadal identity. These observations could be relevant to the observation that PMAH with ARMC5 mutations abnormally express a number of gonadal markers. Altogether these findings demonstrate the need for studies integrating analysis of patients' data with findings of basic studies on the mechanisms of adrenal development and differentiation.

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S17.2

Genetics of Primary Bilateral Macronodular Adrenal Hyperplasia: when and what to test

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France.

Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) consists of bilateral development of adrenocortical macronodules causing various level of cortisol excess independently of circulating ACTH. It can be diagnosed after investigations of clinical signs of Cushing's syndrome, but nowadays more often after the investigation of an adrenal incidentaloma in patients with sub-clinical Cushing. Indeed, 10 to 15% of adrenal incidentalomas are bilateral, corresponding mostly to PBMAH. Several observations suggest a genetic origin of PBMAH: case reports of familial forms, the bilateral and multifocal nature of the adrenal nodules. Genes involved in the cAMP/protein kinase A (PKA) signaling pathway, (GNAS) or as modifying gene (PDE11A4) have been reported as causing the disease. In rare cases PBMAH is observed in patients with hereditary familial tumor syndromes including adenomatous polyposis coli gene (APC), MEN1 (Menin) and Hereditary Leiomyomatosis and Renal Cell Cancer (fumarate hydratase). However, most PBMAH patients do not present with such syndromic associations. In these more common patients the use of combined pan-genomic approaches led to the identification of a new tumor suppressor gene, ARMC5, as a frequent cause of sporadic or familial PBMAH (25–50% in the different series). This demonstrates that PBMAH is often genetically determined and brought some new perspectives for early diagnosis of the disease. Genetic screening for ARMC5 germline mutation could help better diagnosis and classification of patients with PBMAH. Familial screening would lead to the identification of the relatives of an index case with ARMC5 mutation at risk of Cushing's syndrome development. Prospective follow-up will allow a better analysis of the development of PBMAH in such families. In conclusion, the genetic origin of PBMAH is now demonstrated in a significant proportion of the cases, offering new perspectives for pathophysiology, therapy and genetic screening.

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S17.3

Diagnosis and Management of Primary Adrenal Macronodular Hyperplasia

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Macronodular adrenal hyperplasia refers to adrenal enlargement by large nodules that may be related to ACTH-dependent or ACTH-independent pathologies. The term Primary Macronodular Adrenal Hyperplasia (PMAH) was recently introduced to replace the term ACTH-independent macronodular adrenal hyperplasia, since in some cases paracrine ACTH production may contribute to cortisol secretion, and also to encompass cases of unilateral macronodular hyperplasia. PMAH is a heterogeneous disease comprising different entities. The diagnostic approach depends on the clinical context. PMAH is rarely detected as part of the evaluation for ACTH-independent Cushing's syndrome. It is more often detected incidentally; in this setting imaging and hormonal characterisation are required. According to the recent ESE and ENS@T guidelines imaging characterisation should be done separately for each lesion since occasionally co-occurrence of different entities, such as adenoma, pheochromocytoma, cyst, myelolipoma or even adrenocortical carcinoma, may be encountered. The most common hormonal alteration is autonomous cortisol secretion (ACS). ACS follows a continuum and is best assessed using the 1-mg overnight dexamethasone suppression test. According to recent guidelines values of $\leq$50 nmol/l (1.8 μg/dl) exclude 'ACS', values of $>$140 nmol/l (5 μg/dl) confirm 'ACS' and values between 51 and 140 nmol/l (1.9–5.0 μg/dl) indicate 'possible ACS'. Additional tests including ACTH levels, midnight cortisol or 24-hr urinary free cortisol may aid in establishing the degree of cortisol excess. In addition, serum 17-hydroxyprogesterone should be measured to exclude congenital adrenal hyperplasia, keeping in mind that increased levels may also represent secretion of steroid precursors from the lesion(s). Testing for adrenal insufficiency may be relevant in some cases (i.e. when imaging suggests bilateral infiltrative disease or haemorrhage). In several occasions, aberrant responses due to illegitimate receptor expression are also encountered by relevant testing. Genetic testing may be offered in selected cases based on recent findings that PMAH is genetically determined. The appropriate management of PMAH remains controversial. Bilateral adrenalectomy is a debilitating option, resulting in lifetime steroid dependency. This is why the recent guidelines suggest against bilateral adrenalectomy in patients with no clinical signs of overt Cushing's syndrome. In selected patients unilateral adrenalectomy of the dominant lesion or based on adrenal vein sampling results might be considered. The decision for surgery depends on the degree of hypercortisolism, the presence of co-morbidities, age, general health and patient's preference. In cases where the regulation of cortisol secretion is mediated by aberrant hormone receptors there is some potential for medical therapy.

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Borderline testosterone and metabolic outcomes among sexes: clinical relevance

S18.1

Sex hormones, obesity and type 2 diabetes-is there a link?

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Italy.

The different balance in the sex hormones, androgens and estrogens, is a cardinal aspect of the biology of gender difference and plays a fundamental role in maintaining the physiological state at each age of life. However, the imbalance in sex hormones is involved in some metabolic diseases, particularly type 2 diabetes, with androgens playing an interesting sexually dimorphic role. In particular, the bulk of evidence suggests that hyperandrogenism in women or hypogonadism in men facilitate the appearance of type 2 diabetes mainly via the promotion of metabolically unfavourable changes in body composition. The sexual dimorphism of androgens in the pathophysiology of type 2 diabetes leads to inequalities in both preventive strategies and treatment between women and men. Polycystic ovary syndrome (PCOS) is the most common hyperandrogenic disorder in women with a prevalence in fertile European women of around 6–8%. In these women, hyperandrogenism is associated with chronic anovulation and infertility. The prevalence of insulin resistance, obesity, and the metabolic syndrome in general is also high. In addition, the literature supports the notion that PCOS is associated with an increased susceptibility to develop type 2 diabetes at any age and that androgens are the main link between PCOS and type 2 diabetes. To support this assumption there are only few data that demonstrate that antiandrogenic therapy in women affected by PCOS is able to improve IR, decrease abdominal adiposity and probably prevent metabolic complications such as type 2 diabetes.

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S18.2

Relevant therapies in PCOS

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Serbia.

Although there are many phenotypes of polycystic ovarian syndrome (PCOS), we are mainly talking about three phenotypes: metabolic, hyperandrogenic and reproductive phenotype. Obesity and insulin resistance are the major determinants of the metabolic heterogeneity of patients with PCOS. Certain degree of hepatic insulin resistance exists in PCOS irrespective of obesity. In non-obese PCOS preserved insulin sensitivity in peripheral tissues exists. The presence of obesity is of great importance for the treatment of the syndrome. The most important approach should be made to prevent obesity and abdominal adiposity in non-obese women with PCOS. Lifestyle modification, diet and regular physical activity, and anti-obesity drugs, bariatric surgery may be useful in some obese PCOS. It is still dilemma should metabolic complications influence the choice of treatment for PCOS: insulin sensitizer drugs or COCs. Hyperandrogenic phenotype is the most common form of PCOS. Lifestyle changes in the presence of obesity are first line treatment. Pharmacological agents consist of COCs and antiandrogens or combination. In reproductive phenotype, infrequent or absent ovulation is the predominant problem in PCOS women. The main therapeutic issues for women with PCOS and reproductive dysfunction are treatment of infertility or menstrual regulation in PCOS women who do not desire pregnancy. Weight reduction alone may result in spontaneous ovulation in overweight/obese PCOS women. Induction of ovulation can be achieved either by raising endogenous levels of FSH or by giving exogenous FSH by daily injection. The estrogen receptor antagonist, clomiphene citrate, is first choice treatment for induction of ovulation in PCOS, while other antiestrogens are aromatase inhibitors. Metformin has been reported to improve ovulation rates in PCOS women when given alone or together with clomiphene citrate. A low-dose COC may be the most convenient form of treatment for all menstrual irregularities, although cyclical progestogen is an also reasonable alternative.

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S18.3

Testosterone, obesity and the metabolic syndrome in males-do we need to replace steroids?

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Background
In men with obesity and the metabolic syndrome there is an increased prevalence of low serum testosterone. Overweight and moderate obesity is associated mainly with low total testosterone (T) secondary to decreased concentrations of SHBG, which are strongly inversely associated with indices of adiposity and insulin resistance, and preserved free T levels. In more severe obesity and metabolic abnormalities (often with type 2 diabetes) low total T can be accompanied by low free T, usually without appropriate increase of gonadotropins indicating contribution of altered central regulation of gonadal function, of which the underlying mechanisms remain to be fully elucidated. These observations have raised the question whether treatment with T may be needed or beneficial. The main issues involved will be reviewed.
Main points
Are these men hypogonadal? A large proportion of the men with low total T and preserved free T should not be considered as hypogonadal. Those with low free T might be considered hypogonadal if they also present with symptoms of hypogonadism (e.g. sexual dysfunction). Is low T causal in the risk for – or aggravation of obesity and metabolic syndrome? Although the relation between low T and obesity/metabolic syndrome appear to some extent bidirectional, a critical appraisal of the literature indicates that a causal role of T is likely to be only limited with low T rather the consequence than the cause. Is the low T reversible? Weight loss and improved metabolic control can normalize or improve serum T. What are the effects of T therapy on the evolution of obesity and metabolic syndrome? Pharmacologic treatment with T can reduce fat mass and increase lean mass, which may have indirect favorable effects on metabolic control. A critical appraisal of controlled studies learn that these effects remain rather limited and can have at best a marginal effect besides more specific approaches such as based on lifestyle, more specific pharmacologic treatment or bariatric surgery. Is T therapy effective to treat hypogonadism in obese men or men with metabolic syndrome/type 2 diabetes? Yes treatment is effective although possibly less effective than in lean hypogonadal men. How safe is T therapy in these men? Some safety aspects may require special attention (e.g. risk for venous thromboembolism, sleep apnea).
Conclusion
In the present state-of-the-art obesity and metabolic syndrome as such should not be considered as indications for T therapy. Conversely weight loss and improved metabolic control can normalize low T in men with obesity and metabolic syndrome in the absence of other (organic) causes of hypogonadism. In men with obesity and metabolic syndrome and with established hypogonadism (unequivocally low free T and symptoms) T therapy should be considered if measures intended at reducing weight and improving metabolic control fail to normalize or substantially improve serum freeT.

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New Aspects of Pituitary Regulation

S19.1

Cytoskeleton, pharmacologic resistance and clinical aggressiveness in pituitary tumours

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Italy.

Pituitary tumors, are mostly benign, but may cause significant morbidity in affected patients, including visual and neurologic manifestations from mass-effect, or endocrine syndromes caused by hormone hypersecretion. Dopamine (DA) receptor DRD2 and somatostatin (SS) receptors (SSTRs) represent the main targets of pharmacological treatment of pituitary tumors since they mediate inhibitory effects on both hormone secretion and cell proliferation, and their expression is retained by most of these tumors. Although long acting DA and SS analogs are currently used in the treatment of prolactin (PRL)- and growth hormone (GH)-secreting pituitary tumors, respectively, clinical practice indicates a great variability in the frequency and entity of favourable responses. The molecular basis of the pharmacological resistance as well as of clinical aggressiveness are still poorly understood, and several potential molecular mechanisms have been proposed, including defective expression or genetic alterations of DRD2 and SSTRs, or an impaired signal transduction. Recently, cytoskeleton has emerged as novel player implicated in the complex mechanisms of pharmacological resistance of pituitary tumors to DA and SS. In the past 5 years the speaker's group demonstrated that specific cytoskeleton proteins play a key role both in determining tumor clinical aggressiveness and invasion, and in modulating responsiveness to currently used drugs, by regulating receptor localization/signaling. In particular, we demonstrated a role for cytoskeleton protein filamin A (FLNA) in DRD2 and SSTRs receptors expression and signalling in PRL- and GH- secreting tumors, respectively, first revealing a link between FLNA expression and responsiveness of pituitary tumors to pharmacological therapy. Moreover, another cytoskeleton actin binding protein, cofilin, was shown to be a determinant and potential new biomarker for pituitary tumor invasiveness. In this respect, we recently showed that invasiveness of pituitary tumors is promoted by the activation of cofilin, that can be in turn regulated by DRD2. Indeed, DRD2 agonist reduced migration/invasion and increased phosphorylated inactive cofilin in non-functioning pituitary tumoral cells. The talk will provide an overview of the known molecular events involved in SS and DA resistance, focusing on the role played by cytoskeleton by showing both published and unpublished observations.

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S19.2

What fat does with your pituitary

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Spain.

Adipose tissue is a highly active metabolic organ which, together with its classical role as energy storage depot, releases a wide variety of bioactive molecules with signaling properties, the adipokines, that play central roles in the regulation of energy metabolism and homeostasis, immunity and inflammation. Alterations in both adipokine production and lipid metabolism have been proposed to underlie the metabolic and cardiovascular disorders associated to excess body fat accumulation, including insulin resistance, type 2 diabetes, atherosclerosis, dyslipidemia or hypertension. Notably, adipokines and their receptors are also expressed and regulated in other tissues, including the pituitary. We will discuss findings from our group and others on the regulation and molecular mechanisms underlying the action of three major adipokines, leptin, adiponectin, and resistin, on the pituitary cell types as well as their interaction with the major central and peripheral regulators of these cells. Current knowledge, gained from both *in vitro* studies and animal models, including murine and nonhuman-primate species, and human, supports the occurrence of a pituitary-centered local adipokine circuitry which, together with peripheral (i.e. adipose tissue-produced) signaling molecules, may convey metabolic signals to the somatotropic, corticotropic, and reproductive axes. In sum, the pituitary constitutes a relevant site of action for adipokines which likely act as links in the coordinated regulation of metabolism, growth and reproduction.

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S19.3

How cancer treatment effects your pituitary

Frederique Albarel
France.

In recent years, immunotherapy has transformed the treatment in a number of cancers, including melanoma. It is associated with novel autoimmune side effects including endocrinopathies, among which hypophysitis (0.4–20% with Ipilimumab). We carried out a long-term study in endocrinology and dermatology departments of Marseille to characterise ipilimumab-induced hypophysitis in terms of clinical signs, endocrine profile and imaging, at diagnosis and during follow-up. Fifteen patients, treated for malignant melanoma and who presented ipilimumab-induced hypophysitis, were observed between June 2006 and August 2012 in our centre. Symptoms, pituitary function, and pituitary imaging at diagnosis of hypophysitis and during follow-up were recorded. Of 107 patients treated with ipilimumab, 15 (10 mg/kg in 11/15) presented with hypophysitis (14%) at 9.5 ± 9 weeks (mean $\pm$ S.D.) after treatment start, occurring in 66% after the third infusion. The main initial symptoms were headache ($n=13$) and asthenia ($n=11$). All patients but one had at least one hormonal defect: thyrotroph ($n=13$), gonadotroph ($n=12$), or corticotroph ($n=11$) deficiencies. None had diabetes insipidus. Pituitary imaging showed?a moderately enlarged gland in 12 patients. Clinical symptoms improved rapidly on high-dose glucocorticoids ($n=11$) or physiological replacement doses ($n=4$). At the end of follow-up (median 33.6 months, range 7–53.5), corticotroph deficiency remained in 13 patients, 11 recovered thyrotroph and 10 gonadotroph functions. Pituitary imaging remained abnormal in 11 patients. Ipilimumab-induced hypophysitis is a common side effect with frequent hormonal deficiencies at diagnosis. Usually,

hormonal deficiencies improved, except for corticotroph function. Patients receiving these immunomodulatory therapies should be closely monitored especially by systematic baseline hormone measurements after the third infusion and remain? at risk of adrenal insufficiency in the long-term, needing education about adrenal failure risk. We will compare these results with other large international studies, discuss prognostic factors of hypophysitis due to immune check-point inhibitors, possible mechanisms and recommandations about follow-up and treatment.

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All you need to know about lipodystrophy (*Endorsed by Endocrine Connections*)

S20.1

Lipodystrophy as a model for prevalent insulin resistance

David Savage
UK.

All forms of severe lipodystrophy are associated with features of the metabolic syndrome including insulin resistance, T2DM, NAFLD, dyslipidaemia and cardiovascular disease. The question I will address is if this means that what happens in patients with monogenic forms of lipodystrophy is at all relevant to common forms of insulin resistance and the metabolic syndrome.

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S20.2

Acquired forms of lipodystrophy

Giovanni Ceccarini
Italy.

Acquired lipodystrophies (AL) are syndromes characterized by an irreversible loss of subcutaneous adipose tissue and are conventionally distinct in partial (Barraquer-Simons) or generalized forms (Lawrence Syndrome) based on the pattern of adipose tissue disappearance. Alike to congenital forms, AL exhibit metabolic abnormalities that include insulin resistance, diabetes mellitus, hypertliglycerdidemia, reduced leptin levels, hepatomegaly and steatosis. While in most cases of congenital forms of lipodystrophy a genetic alteration can be identified, the pathogenic mechanism responsible for the acquired disease are unknown. Based on the evidence of increased association between AL and autoimmune disorders a reaction against yet-to-be identified white adipose tissue antigens is postulated but the association with autoimmune diseases is variable and any attempt of classification in this context is challenging. Barraquer-Simons syndrome has usually a milder metabolic derangement that may be associated with hypocomplementemia and presence of a 'C3 nefritic factor' auto-antibody, Lawrence syndrome is frequently characterized by the development of severe metabolic complications sometimes difficult to be controlled by standard medical therapies. Other forms of acquired lipodystrophy are iatrogenic. One example being AL secondary to combination anti-retroviral HIV drug treatment. These drugs affect the health of adipose tissue by different mechanisms: generating mitochondrial toxicity, increasing local inflammation, perturbing adipocyte differentiation or impairing hormonal production or signal transduction. Lipodystrophy may also develop after complex treatment related to bone marrow transplant occurring during childhood. Cytotoxic treatments primarily total body irradiation or graft-versus-host disease by taking place during a window of time very sensitive for the commitment of adipose stem cells may affect the normal development of fat mass causing later on lipodystrophy. Bone marrow transplant-induced lipodystrophy is frequently underestimated. Finally, even rarer forms of paraneoplastic, acquired lipodystrophies have been described.

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S20.3

Lipodystrophies, diagnosis and treatment: a step-by-step approach

David Araujo-Vilar
Spain.

Lipodystrophy syndromes are rare heterogeneous disorders characterized by deficiency of adipose tissue, and, frequently associated, but not always, to severe metabolic abnormalities including diabetes mellitus and dyslipidemia. With the exception of HIV-associated lipodystrophy, the other distinct subtypes of lipodystrophy are very infrequent, so they are considered rare diseases. Lipodystrophy is classified as genetic or acquired and by the distribution of fat loss, which can be generalized or partial. In generalized lipodystrophy, adipose tissue is almost absent in patients, whereas in partial lipodystrophy, lipoatrophy affects only specific anatomical sites, and in some cases, lipohypertrophy appears in other sites. Genetic lipodystrophies include Berardinelli-Seip syndrome and Familial Partial Lipodystrophy, but also many different early aging syndromes (progerias) and specific auto-inflammatory syndromes. In this cases, more than 20 genes associated with lipodystrophy have been identified that may assist in diagnosis. Acquired lipodystrophies include, apart HIV-associated lipodystrophy, Lawrence syndrome, Barraquer-Simons syndrome and bone marrow transplant associated lipodystrophy. Because of its rarity and heterogeneity, lipodystrophy may frequently be unrecognized or misdiagnosed, which is concerning because it is progressive and its complications potentially life threatening. Effective management of lipodystrophy includes lifestyle changes and aggressive, evidence-based treatment of comorbidities. Leptin replacement therapy has been found to improve metabolic parameters, mainly in generalized lipodystrophy. In this presentation, it will be described the clinical features of known types of lipodystrophy, an algorithm for differential diagnosis of lipodystrophy subtypes, and suggest specific steps to recognize and diagnose lipodystrophy in the clinical setting.

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The Dance of Adrenal and Gonads (*Endorsed by Endocrine Connections*)

S21.1

Abstract unavailable

S21.2

Management of phaeochromocytoma during pregnancy

Scott Akker
UK.

Abstract unavailable.

S21.3

Fertility in Congenital Adrenal Hyperplasia

Blazej Meczekalski
Poland.

Congenital adrenal hyperplasia (CAH) is defined as several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands. Fertility in women with CAH is essential and underestimated clinical problem. According to current studies patients with classic form of CAH due to 21-hydroxylase deficiency have lower fertility rate that correlate with the severity of mutation. It has complex background which is related to hormonal imbalance, surgery consequences psychological and sexual problems. Menstrual irregularities and anovulation occur frequently in CAH women affecting from 30 to 68% patients. Subfertility problems are milder in patients with nonclassic form of 21-hydroxylase deficiency. Some of these women conceive without treatment. Other women with anovulatory cycles respond to glucocorticoid alone or combined clomiphene citrate. Women with CAH present also higher risk of spontanous abortion than healthy women. Numerous studies reported that glucocorticoid treatment can lower the risk of spontanouse abortion. Males with CAH also may present impaired gonadal function and infertility.CAH patients with fertility problems should be consulted and properly treat.

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The fatty bone

S22.1

Abstract unavailable

S22.2

Bone marrow adipose tissue: starving for attention

William Cawthorn
UK.

Bone marrow adipose tissue (BMAT) accounts for up to 70% of bone marrow volume and over 10% of total adipose mass in lean, healthy humans. BMAT further increases in diverse clinical conditions, including ageing, osteoporosis, obesity/diabetes, glucocorticoid treatment, cancer therapy and, strikingly, during caloric restriction. Many of these conditions are also associated with bone loss and increased fracture risk, and therefore it has been suggested that BMAT might directly impact skeletal remodelling. Recent studies also support a role for bone marrow adipocytes in modulating haematopoiesis, fracture repair and progression of skeletal metastases or myeloid tumours. However, study of BMAT has been relatively limited, and therefore the formation and function of bone marrow adipocytes remains poorly understood. We previously revealed that, during caloric restriction, BMAT contributes to increased circulating levels of adiponectin, a hormone with diverse cardio-metabolic and anti-inflammatory effects. Thus, like white adipose tissue, BMAT is an endocrine organ that can exert systemic effects. My lab is now building on this finding by further investigating the causes and consequences of BMAT formation, in particular during caloric restriction. Our goal is to determine how BMAT impacts metabolic and skeletal health. By combining preclinical models, advanced imaging approaches and clinical sample analyses, our research is beginning to reveal new insights into metabolic and endocrine functions of BMAT; the mechanisms contributing to BMAT formation; and the relationship between BMAT accumulation, bone loss and metabolic health.

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S22.3

Cross-talk between bone marrow and peripheral adipose tissue in man

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Previous studies demonstrate unexpectly high human fat cell turnover. About 10% of the total peripheral fat cell pool is renewed every year. In relative terms this turnover is two-fold increased in obesity but reduced in subjects with pernicious adipose morphology (few but large fat cells). High turnover necessitates a renewable source of adipocyte precursors. Two independent studies, using bone marrow transplanted patients as model, demonstrated important contribution of bone marrow precursors to peripheral generation of fat cells. This input occurs throughout the human life span from infancy and onwards. Itis markedly increased among obese subjects where up to 40% of the peripheral fat cells are generated by the bone marrow. Recent studies using advanced FACS sorting and single cell gene expression measures suggest that there is a uniform pool of fat cell precursors in peripheral adipose tissue, indicating that local and bone marrow derived precursors are of the same origin. Thus, cross-talk between bone marrow and peripheral adipose tissue in the generation of fat cells is an important regulatory factor behind formation of human adipose tissue mass and morphology.

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Pre-diabetes

S23.1

Abstract unavailable

S23.2

Abstract unavailable

S23.3

Treatment of Pre-Type 2 Diabetes

Riccardo Bonadonna
Italy.

Pre-Type 2 Diabetes has not a commonly shared definition. In this talk, the term will be used to indicate people with impaired fasting glucose and/or impaired glucose tolerance and no evidence of pancreatic beta cell autoimmunity. These people are known to be at increased risk of cardiovascular disease/mortality, yet it it is still unclear whether this abnormal risk can be accounted for by the concomitant presence of well recognized risk indicators/factors, most of which are collected under the umbrella of the Metabolic Syndrome. By the same token, there is no known specific treatment of this increased risk beyond the therapies used for the single known risk factors (therapeutic lifestyle changes, therapies for obesity, dyslipidemia, hypertension, etc.). Type 2 Pre-Diabetes also is a high risk condition for type 2 diabetes. Several clinical trials have documented that primary prevention (and often reversal to normal fasting glucose and normal glucose tolerance) of type 2 diabetes in these people can be achieved by as diverse tools as therapeutic lifestyle changes, or metformin, or acarbose, or pioglitazone, or bariatric surgery etc. In many instances, it is somewhat unclear whether the improvement should be ascribed to the effects of early treatment of diabetes or to a genuine modification of the natural history of the disease. However, beneficial effects may be detected even several years after quitting the preventative intervention. Although therapeutic lifestyle changes should be the mainstay of type 2 diabetes primary prevention, they are not as effectively implemented in standard clinical care as they should, possibly owing to costs and a number of hurdles that both the patient and the health care provider need to overcome. Nevertheless, the agenda of type 2 diabetes worldwide will never meet the challenge of type 2 diabetes pandemics without vast and effective programs of primary prevention.

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Ups and downs of hypothalamo-pituitary hormones

S24.1

How Does Pituitary Release its Hormones?

Patrice Mollard
France.

A current challenge in physiology/pathology is translating cell-transduction processes identified *in vitro* into the living organism, especially where cell-cell interaction and dynamics have key functional roles. The pituitary gland, regulating a diverse range of essential physiological functions, exemplifies this challenge: stimulation from the brain is relayed as variable hormone pulses (the hypothalamic-pituitary (HP) system), which are decoded by peripheral organs into differential effects. The stimulatory inputs and intermediary/final secretory output of the HP system have impressive differences in time-scale and the number of cells involved: a few thousand hypothalamic neurons with signalling

frequencies in the millisecond range drive hundreds of thousands of pituitary cells to secrete hormone pulses over a period of hours. These features of the HP system are conserved across a diverse range of mammals. However, how pituitary networks transform hypothalamic inputs into hormone pulses *in vivo* was unknown. Using newly-developed techniques for imaging and manipulating cells *in vivo*, namely in freely-behaving mouse models, we unveiled how the pituitary somatotroph network translates its hypothalamic inputs into GH pulses in the bloodstream.

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S24.2

Peripheral activities of growth hormone-releasing hormone (GHRH)

Riccarda Granata
Italy.

Growth hormone-releasing hormone (GHRH) is synthesized in hypothalamic neurons and regulates the secretion of growth hormone (GH) from the pituitary gland. GHRH also displays extra-pituitary activities in a variety of cells and organs expressing both GHRH, GHRH receptor (GHRH-R) and its splice variants (SVs). These include, among others, the retina, pancreas, kidney, skeletal muscle and heart. In the heart, we have demonstrated that GHRH(1-44)NH2 exerts survival and antihypertrophic effects *in vitro* in murine cardiomyocytes and human induced pluripotent stem cell (iPSC)-derived cardiomyocytes, improves heart function and reduces myocardial infarction (MI) in isolated rat hearts. Moreover, we and others have shown that in murine and swine *in vivo* models, agonistic analogs of GHRH, such as MR-409, counteract maladaptive hypertrophy, improve heart function and protect against ischemic injury, suggesting potential therapeutic role in heart failure and regeneration after myocardial infarction. In tumors, GHRH acts as an autocrine/paracrine growth factor and stimulates growth of various cancers. In the last years, many antagonists of GHRH have been synthesized, with potent inhibitory effects on growth of various tumors, including breast, prostate, lung and gastric cancer. Our recent findings indicate that GHRH antagonists MIA602 and MIA690, either alone or in combination with chemotherapics, potently inhibit the growth of human malignant pleural mesothelioma (MPM) cell lines and primary mesothelioma cells *in vitro*, through induction of apoptosis and inhibition of proliferative and survival pathways. Thus, GHRH antagonists may be considered as additional tools for new therapeutic approaches in MPM, for which an effective therapy remains to be established.

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S24.3

The role of pituitary hormones (among others) in the generation of metabolic stress responses

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Denmark.

Throughout evolution survival of humanity has relied on the ability to cope with stress, such as fasting, exercise, injury and inflammation. In general these conditions generate a metabolic stress response with release of stress hormones (adrenaline, glucagon, cortisol and growth hormone(GH)) and mobilisation of all major fuel sources - lipids, protein and carbohydrate. In addition bacterial ingredients (eg endotoxin/lipopolysaccharide (LPS)) and cytokines (TNF-alfa, interleukins) have independent metabolic effects including liberation of fat and protein from adipose tissue and muscle and induction of fever('exogenous and endogenous pyrogens'). The exact mechanisms triggering the release of stress hormones are uncertain. An increase in body temperature, whether induced by pyrogens (fever), exercise or heating with hot water, initiates hypersecretion of stress hormones, suggesting that the thermoregulatory unit in the preoptic part of hypothalamus is involved. The metabolic stress response may be divided into a rapid 'fight-or-flight' component, primarily driven by adrenaline and glucagon and a more slow component, driven by cortisol and GH, both being characterised by overall catabolism and increased levels of lactate and ketone body stress metabolites. Infusion studies have shown that: (i) adrenaline, cortisol and GH increase the release of fatty acids and induce insulin resistance (ii) glucagon and cortisol increase protein breakdown and urea formation (iii) all four hormones increase endogenous glucose production and (iv) GH preserves protein by decreasing protein breakdown and urea formation. To test the role of the pituitary gland during metabolic stress we have compared metabolic responses to LPS and TNF-alfa in hypopituitary and control subjects - these studies showed that HP patients had a much lesser increase in lipolysis, protein breakdown and urea formation and that intact pituitary function and appropriate cortisol and GH responses are crucial for a full metabolic stress response.

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Late Breaking

S25.1

Extracellular Vesicles: from waste-containers to new opportunities

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Spain.

The term Extracellular Vesicles (EVs) encompasses all those vesicular structures (surrounded by a cell membrane) released into the extracellular environment. Virtually all cells are capable of producing EVs through highly conserved mechanisms in evolution. These vesicles serve as a communication channel between different cells of the organism due to their capacity to exchange biomolecules, including proteins, lipids, nucleic acids or carbohydrates. Their membranous packaging gives protection to these molecular messengers, and would provide selectivity to reach possibly distant cells in the organism. Although described in the 80's, the interest in EVs re-emerged in 90's with the description of their ability to present antigens and thus amplify the immune response. Later, the observation that RNA was contained in vesicles pointed to their role as mediators of intercellular communication. Also, as EV composition is dependent on active mechanisms of protein and nucleic acids recruitment, the presence of specific characteristics on the released material spotted on the search for biomarkers of several diseases. Several studies provided evidence that EVs in biological fluids are good source of potential biomarkers for metabolic diseases. Yet, their use as diagnostic and prognostic biomarkers in clinical practice still needs further validation. Importantly, although different isolation methods have been developed for the study of EVs, most of them do not preclude the presence of non-vesicular contaminants. Therefore, it is still necessary to define a consensus technique to overcome the variability of results obtained depending on the technique used. Ideally, this technique must take into account the final objective of the EV preparation (biomarker determination, therapeutic approach, …). An overview of EVs, from their description, methods of isolation and analysis, and application in biomarker discovery will be discussed.

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S25.2

Senescence-associated reprogramming promotes cancer stemness

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Germany.

Oncogenic activation and anticancer therapies are known to evoke – especially if apoptotic cell death is no longer available – cellular senescence as another stress-responsive safeguard and ultimate cell-cycle exit program in (pre-)malignant cells. Hence, oncogene-induced senescence (OIS) and therapy-induced senescence (TIS) are considered to operate as important anti-tumor principles. However, we previously reported (Dörr-JR *et al.*, Nature, 2013) that secondary, 'senolytic' elimination of TIS cancer cells improves long-term outcome to therapy, thereby suggesting that lastingly persistent senescent cells might be harmful. Driven by the intriguing overlap of numerous pathway mediators relevant in both stem cell and senescence signaling, we now observed in lymphoma and other cancer types reprogramming of senescent cancer cells into a latent adult tissue stem cell state. Strikingly, these senescent cells exerted their gained stemness upon enforced or spontaneous cell-cycle re-entry out of senescence. As the pivotal underlying mechanism, we identified epigenetic reprogramming into a permissive state for active Wnt signaling, which is maintained in a small but stable fraction of the tumor cells post-senescence. Exploiting a non-stem bulk leukemia model, we found cells incapable of re-initiating the disease to convert into leukemia stem cells via temporarily entering TIS. In this late-breaking presentation, strategies to induce or restore senescence in the first place, and conceptually novel approaches to selectively eliminate these senescent cancer cells subsequently for improved long-term tumor control will be presented and discussed.

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S25.3

LEAP2 is an Endogenous Antagonist of the Ghrelin Receptor

Daniel Kaplan
USA.

Ghrelin, an appetite-stimulatory hormone secreted by the stomach, was discovered as a ligand for the growth hormone secretagogue receptor (GHSR). Through GHSR, ghrelin stimulates growth hormone (GH) secretion, a function that evolved to protect against starvation-induced hypoglycemia. Though the biology mediated by ghrelin has been described in great detail, regulation of ghrelin action is poorly understood. Here, we report the discovery of liver-expressed antimicrobial peptide 2 (LEAP2) as an endogenous antagonist of GHSR. LEAP2 is produced in the liver and small intestine, and its secretion is suppressed by fasting. LEAP2 fully inhibits GHSR activation by ghrelin and blocks the major effects of ghrelin *in vivo*, including food intake, GH release, and maintenance of viable glucose levels during chronic caloric restriction. In contrast, neutralizing antibodies that block endogenous LEAP2 function enhance ghrelin action *in vivo*. Our findings reveal a mechanism for fine tuning ghrelin action in response to changing environmental conditions.

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Cortisol: Too much of a Good Thing

S26.1

Genetics of Cushing's disease

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USA.

Corticotropinomas represent only a small fraction of all the cases of pituitary adenomas, yet they have the potential for great morbidity and mortality. Presenting clinically as Cushing's disease (CD), corticotropinomas are characterized at the molecular level by resistance to glucocorticoid negative feedback, dysregulation of proteins controlling cell cycle progression, and overexpression of pathways that sustain overactive ACTH production and secretion. Until recently, little was known about the genetic defects underlying most of the cases of CD, and the discovery of somatic gain-of-function USP8 mutations as the most common genetic abnormality in corticotropinomas has represented a breakthrough in the field. Nevertheless, germline causes of CD remain greatly unknown. The vast majority of the patients present sporadically, but CD is part of a growing number of syndromes of isolated pituitary adenoma or multiple endocrine and non-endocrine neoplasia. Although rare, familial forms of CD should be overrepresented among young-onset cases, therefore, pediatric patients represent an excellent opportunity for gene discovery. This talk will review the most recent findings in genetic causes of CD, placed in the context of a large cohort of more than 200 pediatric patients studied at a single center during the last 20 years. The frequency of multiple genetic causes of CD in such setting will be presented, while exploring currently ongoing research projects and discussing new avenues for further investigation. Understanding the genetic defects driving corticotroph tumorigenesis should lead to unraveling novel therapeutic targets. This will hopefully be translated into more efficient strategies for the medical treatment of patients with CD.

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S26.2

Hypercortisolism and the brain

Nic van der Wee
The Netherlands.

Background
Alongside various physical symptoms, patients with high levels of cortisol, such as typically found in Cushing's disease, often display a wide variety of neuropsychiatric symptoms such as depression, psychosis, mania and cognitive impairments. This indicates involvement of the central nervous system in hypercortisolism.
Methods
Various neuroimaging approaches can be used to examine the effects of hypercortisolism on the brain. The frequently used structural magnetic resonance imaging (MRI) techniques allow detection of alterations of volume or shape of brain regions or in local grey matter volume. Common functional MRI (fMRI) designs detect changes in task related activity. More novel approaches, such as resting-state fMRI or diffusion tensor imaging (DTI) focus on structural and functional connectivity between brain regions.
Results
Early structural MRI studies in Cushing's disease found indications for bilateral reductions of the volume of the hippocampus and the cerebellum. More recent structural MRI studies also implicate the amygdala and the medial prefrontal cortex, not only in active, but also in remitted hypercortisolism. In addition, specific diffuse alterations of white matter connectivity, suggestive of demyelination were found in both conditions. Furthermore, patients also show disturbed resting state functional connectivity, altered activity during the processing of emotional information and changes in markers of neuronal viability. Data suggests partial reversibility of these functional and structural MRI findings, but longitudinal studies are lacking.
Conclusion
Patients with current or past (endogenous) hypercortisolism show alterations of structure, activity and connectivity of brain circuitry involved in emotion regulation and cognitive processes. Longitudinal studies are lacking and translational approaches are needed to further elucidate the underlying processes.

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S26.3

Differentiating Cushing from Pseudo-Cushing

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Background
Pseudo-Cushing's syndrome (PCS) constitutes a group of physiological or non-physiological medical conditions that mimic Cushing's syndrome (CS) clinical features along with a mild biochemical hypercortisolaemia which remains under a physiological feedback hormonal control. Physiological conditions such as pregnancy, surgical or emotional stress, severe illness, intense chronic exercise, and non-physiological as chronic alcoholism, obesity, metabolic syndrome, poorly controlled diabetes mellitus, major depression, malnutrition, anorexia nervosa represent a PCS.
Aim of this presentation
The aim of this presentation is to unravel the diagnostic tools that are currently available to differentiate CS from PCS.
Methodology
Differential diagnosis is often challenging since we now frequently see mild cases of CS while symptoms and signs of CS may be present in PCS.
Results
Clinical examination is helpful when signs such as easy bruising without an obvious trauma, facial plethora, proximal myopathy, reddish purple striae (1 cm wide), unexplained osteoporosis or weight gain with decreasing growth in children, suggest hypercortisolism. Biochemical diagnosis in CS includes late-night salivary cortisol (LN-SC), dexamethasone suppression test (DSST), and urinary free cortisol (UFC) as screening tests. However, UFC may be elevated in severe obesity but not in mild or cyclic CS. Dexamethasone suppression-corticotropin-releasing hormone (CRH) test combining the low-dose DSST and the CRH test is based on the fact that dexamethasone suppresses serum cortisol levels in normal individuals as in a small number of those with Cushing's disease (CD), but following CRH administration only patients with CD respond with an increase in ACTH and cortisol secretion. Moreover, desmopressin stimulation test is based on the fact that the vasopressin analogue desmopressin (1-deamino-8D-arginine vasopressin, DDAVP) stimulates ACTH release, representing an aberrant response of neoplastic cells in patients with CD but not in patients with PCS. Finally, LN-SC or midnight serum cortisol demonstrated high diagnostic accuracy in differentiating patients with PCS compared to patients with CS.
Conclusion
Since there is no biochemical suppression or stimulation test and no individual clinical feature that may warrant a 100% diagnostic accuracy for the discrimination of CS from PCS, their combination probably represents the most useful tool for the physicians to challenge this differential diagnosis.

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Emerging treatments in osteoporosis

S27.1

Abstract unavailable

S27.2

Novel therapies: PTH-related protein and sclerostin inhibition

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The treatment of osteoporosis consists of either antiresorptive or anabolic approaches. While there are a number of antiresorptive options available (i.e. bisphosphonates, SERMs and denosumab), teriparatide (PTH 1-34) is currently the only bone anabolic agent approved in the EU. The PTH-related protein (PTHrP) analogue abaloparatide and the sclerostin antibody romosozumab are two anabolic agents that are in the approval process for the treatment of postmenopausal osteoporosis. In the phase 3 ACTIVE trial abaloparatide was compared to placebo and teriparatide for 18 months in postmenopausal women who had already experienced an osteoporotic fracture. Abaloparatide successfully reduced the rate of new vertebral fractures by 86% compared to placebo. Furthermore, abaloparatide achieved greater BMD increases at all measured sites compared to placebo and teriparatide. Based on these results, abaloparatide was FDA approved in April 2017. Romosozumab is a monoclonal antibody that targets the Wnt inhibitor sclerostin. Two phase 3 trials of romosozumab for the treatment of postmenopausal osteoporosis have been completed. The FRAME trial was placebo controlled. After 12 months of romosozumab or placebo, patients were switched to an additional 12 months of denosumab in both groups. The ARCH trial included women that had already experienced a vertebral fracture and compared 12 months of romosozumab to alendronate. After 12 months all patients were switched to open label alendronate. Both trials successfully reached their primary endpoint by reducing vertebral fractures by 75% (FRAME trial) and 48% (ARCH trial) at 24 months, respectively. In the ARCH trial a safety signal for cardiovascular events, not previously seen in other romosozumab trials, was detected with a numerical imbalance between romosozumab (2.5%) and alendronate (1.9%). These results warranted further analyses and have prolonged the approval process for romosozumab.

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S27.3

Sequential and combination therapy for osteoporosis.

Zhanna Belaya
Russia.

Over past years various treatment options for osteoporosis have become available and withdrawn due to side effects or insufficient efficacy. This summary reviews sequential and combination therapy for osteoporosis with the currently approved first line treatments such as potent antiresorbtive (nitrogen-containing bisphosphonates (BP), denosumab (DM)) or anabolic agents (teriparatide, abaloparatide). We assume that all medications are taken with vitamin D and calcium supplements. The differences in mechanisms of action between BP and DM provide explanations in clinical outcome and opportunities in sequential therapy. BP attach to hydroxyapatite preferably on metabolically active bone surfaces, where they are 'ingested' by osteoclasts and promote osteoclast apoptosis. BP can remain in bone tissue for up to 10 years. DM acts by binding to and inhibiting RANKL in circulation, leading to the loss of mature osteoclast formation. DM accesses every bone remodeling unit within circulation and its distribution does not depend on the activity of bone remodeling. In clinical trials, DM given after BP continued to increase bone mineral density (BMD) and produced significantly greater gains in BMD at all measured sites when compared to all BP. Consequently, DM can be given after BP when the treatment goal in BMD gain is not achieved. However, BP also should be given after DM discontinuation to prevent BMD loss. Both VERO and ARCH studies proved that anabolic treatment for osteoporosis is more effective than BP at preventing vertebral fractures in a high risk population (with previous vertebral fractures) in both treatment-naïve or BP treated patients. Consequently, anabolic treatment should be considered either as a first-line treatment in patients with previous vertebral fractures or in case a low-traumatic fracture occurs while on BP treatment. However, the duration of anabolic treatment is limited and requires antiresorbtive medication after discontinuation. The sequential treatment approach in osteoporosis is slightly limited with the result of DATA study, which showed that switching to teriparatide after DM lead to BMD loss and should be considered with caution. According to the DATA study, teriparatide combined with DM gives better BMD gain than both treatments alone. This is the only currently recommended approach using combined treatment in osteoporosis which remains controversial because of the high cost and lack of evidence regarding antifracture benefit.

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Endocrinology Meets Immunology

S28.1

Abstract unavailable

S28.2

Abstract unavailable

S28.3

Immunotherapy Related Endocrinopathies

Mark Vanderpump
UK.

Recent advances in immunology have resulted in the development of new classes of immune-modulatory therapy in the management of cancers and an increased overall survival for various cancers. Immune checkpoint direct antibodies block intrinsic down-regulators of immunity, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1). As an inevitable consequence of increasing the activity of the immune system, immune checkpoint blockade result in immune-related adverse events (IRAEs). Although any organ can be affected, IRAEs commonly involve endocrine glands. Endocrinopathies described include hypophysitis with or without hypopituitarism, thyroid dysfunction (transient thyrotoxicosis, transient or permanent hypothyroidism, orbitopathy) and rarely adrenalitis and autoimmune insulin-requiring diabetes. The management of hypophysitis, a potentially life-threatening complication, primarily involves replacement of deficient pituitary hormones and consideration of drug discontinuation and/or immunosuppressive glucocorticoid therapy. Hyperthyroidism, most commonly due to a transient thyroiditis than Graves' disease, should be managed conventionally. Primary hypothyroidism, hypoadrenalism and autoimmune diabetes should also be treated with conventional replacement. IRAEs usually develop within the first few weeks to months after treatment initiation but can present after cessation of therapy. Some studies suggest that patients with IRAEs have higher tumour response rates than those without such events, but these findings remain controversial and the development of IRAEs is not required for treatment benefit. There are no clinical or biochemical features which predict those patients who will develop IRAEs. In the absence of clinical trials, management strategies for effectively monitoring or managing specific IRAEs remains variable and are currently based on consensus opinion.

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Thyroid hormone action: regulation and clinical implications

S29.1

Tissue-specific regulation of thyroid hormone action

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Hungary.

Thyroid hormone (TH) signalling regulates tissues function in virtually all organs and exerts a striking impact on brain development and function. The major secretory product of the human thyroid gland is thyroxine (T4), a stable pro-hormone. In order to bind the TH receptor TR, T4 needs to get converted to T3 by deiodination. The hypothalamo-pituitary-thyroid (HPT) axis controls circulating TH levels, that show remarkable stability. However, tissue TH action undergoes vigorous changes that is achieved by cell-type specific customization of TH availability by local TH metabolizing deiodinase enzymes and transporters. Region-specific regulation of TH action in the brain is critical to regulate TH-dependent brain function. Importantly, this process is also essential for the generation of T3-mediated negative feedback on hypophysiotropic TRH-synthesizing neurons that are located in the paraventricular nucleus. In the hypothalamus, regulation of region-specific TH action functionally overlaps with central regulation of the HPT axis. Therefore, regulation of hypothalamic TH economy is hallmarked by unique features represented by highly compartmentalised neuro-glial mechanisms. These include TH activation via type 2 deiodinase (D2) in tanycytes, lining the lateral wall and the floor of the third ventricle of the mediobasal hypothalamus; and type 3 deiodinase-mediated TH inactivation that fine tunes TH availability in neurosecretory neurons in a phenotype specific manner. We will discuss recent findings on neuropeptide and ubiquitination mediated regulation of hypothalamic TH metabolism. These studies allow better understanding of hypothalamus-specific TH activation; its impact on the HPT axis; and its hypothalamic and systemic consequences during TH supplementation. Finally, we will discuss the hypothalamic pathogenesis and tissue-specific TH availability during lipopolysaccharide-induced nonthyroidal illness syndrome based on data obtained on our recently generated TH action indicator (THAI) transgenic mouse, allowing the assessment of tissue-specific TH action in the intact context of endogenously expressed regulatory factors of TH economy.

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S29.2

Thyroid hormone economy in human aging

Diana van Heemst
The Netherlands.

Thyroid hormones play an important role in all stages of life, including old age. Several differences have been observed in thyroid function parameters with age, including an increase in circulating thyroid stimulating hormone (TSH) levels gradually increase with age. In order to identify determinants of human longevity, the Leiden Longevity Study (LLS) included 421 families with at least two long-lived Caucasian siblings fulfilling the age criteria (men $\geq$89 years and women $\geq$91 years) without selection on health or demographics. We also included the offspring of these long-lived siblings and partners thereof, serving as a control group. Previously, we found higher TSH secretion and a stronger TSH-fT3 temporal relationship in the offspring compared to controls. Our current research which is performed in the THYRAGE (Resetting the THYRoid axis for prevention of AGE-related diseases and co-morbidities) consortium is devoted at disentangling of the role of thyroid hormone economy in human longevity and age-related diseases, including maintenance and functional decline of the central nervous system, and the musculoskeletal system.

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S29.3

Abstract unavailable.

Disorders of Sexual Development (DSD)

S30.1

Abstract unavailable.

S30.2

Atypical Genital Development and Hypospadias: a Pediatric Urology perspective from Etiology to Surgery

Nicolas Kalfa
France.

Atypical Genital Development (AGD) is defined as congenital conditions within which the development of chromosomal, gonadal and anatomic sex is atypical. Hypospadias represents one of the aspects of the spectrum of AGD and its less severe for in case of isolated hypospadias. Despite the Consensus Meeting in Chicago in 2005 and an overall accepted classification of ADG, numerous questions remain to be solved. The etiology of AGD and hypospadias is still unclear at the crossroads of genetics, endocrinology and environment. Environmental disrupting chemicals are particularly suspected to participate in the occurrence and the increasing incidence of genital malformations in boys. Controlled prospective studies in patients without any genetic defects on the main candidate genes strongly support the role of environment. Surgical repair of these genital defects is a challenge that aims to provide both a good functional (urinary and sexual) and cosmetic outcome. Technical aspects as well as the age of repair may be of importance. Long-term outcome is still difficult to evaluate due to the heterogeneity of the series, to a wide range of phenotypes and to the evaluation of no-longer used techniques. Prenatal diagnosis of AGD is increasing. Identification of atypical genitalia by prenatal ultrasound remains challenging compared to other defects. Reliable predictive factors to screen the most severe forms of genital malformations are still lacking. What is the clinical spectrum of genital defects diagnosed before birth? What is the rate of associated defects? How to identify predictive factors for severe phenotypes at birth? The late surgery and the no surgery alternatives have recently been proposed. The absence of vital emergency, the absence of the patient's point of view in the early infancy and the questionable value of the parents 'choice lead to new ethical, political and societal questions. But the no surgery option remains a choice. Pros and cons of each attitude remain a hot topic.

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S30.3

Brain structure and function in gender dysphoria

Julie Bakker
Belgium.

The concept of gender identity is uniquely human. Hence we are left with the phenomenon of men and women suffering from Gender Dysphoria (GD) also known as transsexualism to study the origins of gender identity in humans. It has been hypothesized that atypical levels of sex steroids during a perinatal critical period of neuronal sexual differentiation may be involved in the development of GD. In order to test this hypothesis, we investigated brain structure and function in individuals diagnosed with GD using magnetic resonance imaging (MRI). Since GD is often diagnosed in childhood and puberty has been proposed to be an additional organizational period in brain differentiation, we included both prepubertal children and adolescents with GD in our studies. First, we measured brain activation upon exposure to androstadienone, a putative male chemo-signal which evokes sex differences in hypothalamic activation (women $>$ men). We found that hypothalamic responses of both adolescent girls and boys diagnosed

with GD were more similar to their experienced gender than their birth sex, which supports the hypothesis of a sex-atypical brain differentiation in these individuals. At the structural level, we analyzed both regional gray matter (GM) volumes and white matter (WM) microstructure using diffusion tensor imaging. In cis-gender girls, larger GM volumes were observed in the bilateral superior medial frontal and left pre/postcentral cortex, while cis-gender boys had more volume in the bilateral superior-posterior cerebellum and hypothalamus. Within these regions of interest representing sexually dimorphic brain structures, GM volumes of both GD groups deviated from the volumetric characteristics of their birth sex towards those of individuals sharing their gender identity. Furthermore, we found intermediate patterns in WM microstructure in adolescent boys with GD, but only sex-typical ones in adolescent girls with GD. These results on brain structure are thus partially in line with a sex-atypical differentiation of the brain during early development in individuals with GD, but might also suggest that other mechanisms are involved. Indeed, using resting state MRI, we observed GD-specific functional connectivity in the visual network in adolescent girls with GD. The latter is in support of a more recent hypothesis on alterations in brain networks important for own body perception and self-referential processing in individuals with GD.

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Special Symposium: Bone & Vitamin D (*Endorsed by Endocrine Connections*)

SS1.1

Free and bound vitamin D and health outcomes.

Inez Schoenmakers
Norwich.

Research into the role of vitamin D in human health has significantly increased. Best known for its role in calcium and bone metabolism, it is now also acknowledged to play a role in non-calcaemic processes, including muscle and immune function. For many of these, randomised controlled trials are underway and mechanisms are only partly understood. The plasma concentration of 25-Hydroxy-vitamin D (25OHD) is considered the best marker of vitamin D status. The free fraction of 25OHD has been proposed as an additional or better measure of tissue availability. Free 25OHD is calculated from total 25OHD, vitamin D binding protein (DBP) and albumin concentrations or directly measured by ELISA. The free hormone theory states that only the free fraction can enter cells. This may however not fully apply to 25OHD since several organs express a megalin-mediated internalisation mechanism for DBP bound metabolites. In healthy people, plasma total and free 25OHD are highly correlated. Specific physiological and pathological conditions are associated with alterations of plasma DBP and the relationship between total and free 25OHD, such as renal disease and pregnancy. The impact of these variations on tissue 25OHD availability is unclear. Compared to total 25OHD, free 25OHD has been reported to be more strongly associated with PTH, BMD and various non-skeletal or calcaemic outcomes (e.g. risk of various types of cancer) in some but not all reports. There is also conflicting evidence regarding racial differences in the total to free 25OHD ratio. These findings may be confounded by methodological issues in one of the DBP assays used, resulting in pronounced differences in DBP concentrations between GC-genotypes. I will review novel research into vitamin D and the current evidence regarding the potential differences between the relationships of free and total 25OHD with health outcomes and the potential role of DBP concentration and genotype.

DOI: 10.1530/endoabs.56.SS1.1

SS1.2

Vitamin D in critical illness

Karin Amrein
Austria.

Depending on definition and population, vitamin D deficiency (usually 25(OH)D $\leq$20 ng/ml) is present in 30–60% of ICU patients worldwide. Since 2009, observational studies have clearly shown that vitamin D deficiency is linked to excess morbidity and mortality in adults and children including increased organ failure. Preliminary data using metabolomics suggest that several biochemical pathways, which are important for redox regulation and immunomodulation, are affected by vitamin D status. So far, worldwide $<$700 patients have been treated in a very limited number of randomized controlled intervention trials, recently summarized in three different meta-analyses. The largest published study to date, the VITdAL-ICU study (n=475) did not find a difference in the primary outcome length of hospital stay between groups, but there was a significant reduction in mortality in the predefined subgroup of patients with severe vitamin D deficiency. The VIOLET study (USA) and our own VITDALIZE study will together recruit more than 5000 acutely ill patients and answer the question if vitamin D is benefitial in critical illness in the next few years. If the results are positive this would have a huge positive impact on the outcome of critically ill patients worldwide and maybe even change the current inconclusive judgment of the importance of vitamin D for the health of human beings in general.

DOI: 10.1530/endoabs.56.SS1.2

SS1.3

The effects of Vitamin D deficiency on macrophages function, cholesterol metabolism and cardiometabolic disease

Carlos Bernal-Mizrachi
USA.

Vitamin D has been shown not only to be important for bone and calcium metabolism but also for homeostasis of critical tissues involved in vascular disease. The vitamin D receptor (VDR) and the 1a-hydroxylase enzyme are present in critical cells implicated in the development of vascular disease. Vitamin D influences multiple mechanisms to decrease vascular inflammation: it suppresses the renin-angiotensin system, promotes endothelial nitric oxide release, decreases vascular inflammatory markers and cholesterol deposition, and imbues immune cells with anti-inflammatory properties. Studies in our mouse models of diet-induced insulin resistance show that vitamin D deficiency or conditional deletion of VDR in macrophages promotes insulin resistance, renin-dependent hypertension, and accelerates atherosclerosis. In type 2 diabetes patients, vitamin D deficiency promotes a pro-inflammatory monocyte phenotype with increased adhesion and migration to endothelial cells. Conversely, 25(OH)D or 1,25(OH)2D3 supplementation in culture suppresses this pro-inflammatory monocyte phenotype and reduces cellular cholesterol content by downregulation of ER stress, suggesting that reduced monocyte vitamin D signaling is a critical mechanism for vascular invasion and atherosclerosis. Human observational studies indicate consistent associations between low 25(OH)D levels and increased cardiovascular disease, but the effects of vitamin D supplementation for prevention are conflicting, and study design limitations preclude adequate conclusions.

DOI: 10.1530/endoabs.56.SS1.3

Guidelines: ESE - ENSAT guidelines on the management of adrenocortical carcinoma in adults

GL1.1

ESE - ENSAT guidelines on the management of adrenocortical carcinoma in adults

Martin Fassnacht
Germany.

In our session we will present for the first time the results of our research and consensus process on the development of clinical practice guideline on adrenocortical carcinoma. A multidisciplinary team of 10 clinical and methodological experts reviewed the entire literature until 31.12.2017 and formulated recommendations on all aspects of the clinical management of adult patients with adrenocortical carcinoma.

DOI: 10.1530/endoabs.56.GL1.1

GL1.2

Abstract unavailable.

GL1.3

Abstract unavailable.

GL1.4

Abstract unavailable.

GL1.5

Abstract unavailable.

GL1.6

Abstract unavailable.

Endo-ERN: concrete examples of added value for patient care

ERN1.1

Introduction, structure, and virtual consultation using the EU-ERN CPMS

Alberto Pereira
The Netherlands.

The mission of the European Reference Network on Rare Endocrine Conditions (Endo-ERN) is to reduce and ultimately abolish inaequalities in care for patients with rare endocrine conditions across Europe. Endo-ERN provides equality between paediatric and adult patients, and is supported by the European Society of Endocrinology and the European Society of Paediatric Endocrinology. In order to achieve Endo-ERN's mission and accomplish the concrete objectives the first year was mainly focused on mapping the knowledge base, innovation capacity, and quality of care for each of the main thematic groups, while the second year is now focused on the stepwise execution/ implementation of the planning that was generated in the 1st year. This includes: i) an educational program that fits with the needs of the Endo- ERN members, ii)(in extend of this support) an e-environment that supports all actions of Endo-ERN, iii) Endo-ERN influence on setting guidelines and research agendas, iv) a functional clinical support Operational Helpdesk to democratise access to high-expertise consultations, that also enables linking to registries, and v) a start with an inter-connected diagnostic laboratory network, and setting the standards. The ERN-IT Platform provides the virtual link for the Networks, and includes the public website, the ERN Collaborative Platform, and the Clinical Patient Management system (CPMS). The CPMS has recently been launched to support the cross-border activities of the ERNs enabling virtual consultations by expert boards. To ensure adequate and efficient use of CPMS an operational helpdesks for paediatric and adult endocrinology in Luebeck and Leiden will be instituted. In addition, CPMS will be piloted for a small group of conditions requiring cross-border input and virtual tools for interpreting complex biochemistry. Lastly, CPMS will be linked to EuRRECa (European Registry for Rare Endocrine Conditions) platform.

DOI: 10.1530/endoabs.56.ERN1.1

ERN1.2

Caring for endocrinology across the life span: DSD and Hypogonadotropic hypogonadism

Olaf Hiort
Germany.

The European Reference Network on Rare Endocrine Conditions (Endo-ERN) was founded to improve access to high-quality health care across Europe for patients with rare hormonal disorders. It is meant to encompass all rare endocrine conditions with an equal distribution of paediatric and adult care. The Main Thematic Group (MTG) 'Sex Development and Maturation' is dedicated to the medical conditions involving the reproductive system in both sexes, including the broad ranges of Disorders of Sex Development (DSD) and hypogonadotropic hypogonadism. Medical issues that require special attention range from prenatal therapy in Congenital Adrenal Hyperplasia (CAH) to diagnosis and possibly gender assessment in DSD conditions as well as to hormonal therapies at the time of pubertal development and reproductive assessment in adulthood. The MTG stems from two previous European networks funded by the Cooperation of Science and Technology (COST) in Horizon 2020. The COST Actions GnRHnetwork and DSDnet recently met with the Endo-ERN MTG in order to discuss the most important issues for future care and also scientific progress. In order to provide a solid basis for the future approaches, the need for laboratory comparability across the life-span was emphasized, as well as the compilation of appropriate patient cohorts for clinical trials. Guidelines will help with the enhancement of common and equal management of patients with these rare conditions. Furthermore, through Endo-ERN and the inclusion of relevant patient advocates, this group will be able to pose with relevant stakeholders in the societal discussions on gender issues and overall management of DSD and intersex conditions. Additionally, the MTG can and will link with scientific projects involving basic science, because research on adequate model systems will always provide the basis for further studies on management in humans.

DOI: 10.1530/endoabs.56.ERN1.2

ERN1.3

ESE Endo-ERN symposium: Patient and family perspectives, Manuela Brösamle, Endo-ERN ePAG

Manuela Brösamle
Germany.

Introduction
The presentation is based on experiences and opinions of CAH patients represented by German AGS parents and patient initiatives.
Meaning of patient and family perspectives
The aim is to provide an overview about wishes and expectations of German CAH patients. A special view will be given to quality of live and influencing factors of treatment.
Examples of family perspectives
The importance and meaning of patient and family perspectives will be discussed using some concrete examples. The examples relate to both male and female patients.
Conclusion
Factors of influence on patient quality of life. Family perspectives are depending on good medical treatment and education from childhood to adulthood and beyond.
Requirements of good family perspectives
Requirements of good family perspectives are for instance education of the patient and availability of specialized physicians.
Next Steps and To Do's
Finally, the presentation will discuss the endeavours faced and which steps should be prioritized to ensure optimal patient way of life.

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New Scientific Approaches

NSA1

Abstract unavailable.

NSA2

A comprehensive map of splicing alterations in small cell lung cancer

Eduardo Eyras
Spain.

Small cell lung cancer (SCLC) is the most aggressive form of lung cancer as it lacks known targets of therapy. 5-year survival is only 5% and patients quickly develop therapy resistance by yet unknown mechanisms. The lack of advances is also related to the fact that SCLC is not part of the ICGC or TCGA cancer genomics projects, and patient material is hard to obtain. SCLC presents frequent amplifications in genes of the MYC family, which are known regulators of splicing factors, but the role of splicing in therapy and resistance is not known yet. We have recently shown that splicing alterations provide new mechanisms of tumor progression [1], and that by analyzing the somatic mutations according to RNA selection processes, new impacts on RNA-processing can be uncovered [2] We have now expanded these efforts to study non-coding variants and RNA-processing alterations in SCLC. We have collected the largest compendium of somatic mutation and RNA-seq data available to date for SCLC samples from multiple sources [3–5]. By integrating this data we have obtained a total of 2.579 splicing altering somatic mutations on 63 samples. Genes with the largest splicing changes included several linked previously with cancer, like LIMS1. Intron retention cases include genes involved in DNA repair, like POLD3; or the NOTCH pathway, like KIT. Among the cryptic junctions showing expression in SCLC we recovered the cases previously reported for RB1 and TP73, plus 86 new ones, including cases in the genes of the Wnt signaling pathway ASPM and CTNND2. This is the largest analysis performed to date of RNA processing alterations in SCLC. The results could lead to the uncovering of novel targets of therapy.

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DOI: 10.1530/endoabs.56.NSA2

NSA3

Reprgrammin strategies to obtain functional endocrine units; focus on the adrenal cortex

Leonardo Guasti
UK.

Primary or secondary adrenal insufficiency (AI) results from adrenal failure or impairment of the hypothalamic-pituitary axis, respectively. In both cases, the cortex fails to secrete sufficient amounts of glucocorticoids and adrenal androgens, but in primary AI the clinical consequences of aldosterone deficiency make this a more lethal condition. The most frequent cause of primary AI is autosomal recessive congenital adrenal hyperplasia (CAH), which results from defects in enzymes involved in steroid biosynthesis. Patients with AI need life-long management with exogenous steroids: this can be challenging as no drug suitably mimics the diurnal pattern of cortisol, and objective variables measuring the quality of replacement therapy are lacking. Fine-tuning of replacement therapy leaves only a narrow margin for improvement: under-replacement can result in severe impairment of well-being and incipient crisis, while even subtle, chronic over-replacement has the potential to contribute to excess morbidity including obesity, osteoporosis, hypertension and impaired glucose tolerance. Therefore, better treatment solutions are urgently needed. The ability to generate donor-specific and functional adrenocortical-like cells would facilitate i) the next generation of cell-based treatments for AI; ii) the modelling of adrenal specific diseases and iii) the testing of personalised interventions on cells derived from patients. We have generated human induced steroidogenic cells (hiSCs) using a variety of human cell sources, such as fibroblasts, blood- and urine-derived. reprogramming was achieved threough forced expression of Steroidogenic Factor-1 and activation of protein kinase-A pathway in the presence of luteinizing hormone- releasing hormone. hiSCs have ultrastructural features resembling steroid-secreting cells, express steroidogenic enzymes and secrete steroid hormones in response to both pharmacological and physiological stimuli. hiSCs can successfully engraft into the mouse kidney capsule and can undergo differentiation when injected intra-adrenally. Importantly, the hypocortisolism of hiSCs derived from patients with adrenal insufficiency due to congenital adrenal hyperplasia can be rescued by expressing the wild-type version of the defective disease-causing enzymes. This technology provides an effective tool with many potential applications to study adrenal pathobiology in a personalized manner and opens venues for the development of precision therapies.

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NSA4

3D visualisation of the HPG axis in mice and humans

Paolo Giacobini
France.

Histology has been a golden tool for biological research for decades. Nevertheless, whole organ histology is extremely time and resource consuming and most of the time impossible due to the distortions and lack of algorithms to correctly align thousands of sections. Light sheet-based microscopy is an important, innovative tool that offers nondestructive optical sectioning of selectively stained thick tissues at a spatial resolution between that of micro MRI and confocal microscopy and high-speed scanning capability. Recently developed tissue clearing methods coupled with laser-scanning microscopy made it possible to explore intact organs and to accurately acquire complete histological information about labeled cells/molecules in large tissues, including their spatial density and distribution. Among those techniques, the process called 3D imaging of solvent-cleared organs (3DISCO), has been proved to be a simple and inexpensive method for 3D analysis of immunolabelled transparent organs in embryonic and postnatal animals. Herein, combining 3DISCO with light-sheet laser-scanning ultramicroscopy, we studied the development and 3D organization of the hypothalamic-pituitary-gonadal axis in several mammalian species. Our 3D data demonstrate that with thorough biochemical optimization, we can now detect morphogenetic processes, cell migration and terminal differentiation during embryonic and postnatal development of mice. Moreover, this technique can be adapted to human tissues for volume imaging during fetal development as well as for the analysis of adult post-mortem tissues. The approach thus opens a novel route for high-resolution studies of brain architecture in mammals in physiological and pathological conditions.

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NSA5

Circulating miRNAs in endocrine tumours

Peter Igaz
Hungary.

The discovery of microRNAs (miRNAs) as the endogenous mediators of RNA interference was a major event in contemporary biomedical research. miRNAs were shown to be involved in the regulation of gene expression affecting several basic physiological and pathological processes as parts of the epigenetic machinery. Differential expression of tissue miRNAs were described in several diseases including tumours. In tumours, up- and down-regulated miRNAs can be classified as oncogenes or tumour suppressors, and miRNAs were established as markers of malignancy and prognosis. Novel findings have shown that miRNAs are found in body fluids, as well. miRNAs can be released via passive route (necrosis, inflammation) or by active secretion either in membrane vesicles (exosomes, microvesicles) or in association with macromolecular complexes (Argonaute 2 protein, or high-density lipoprotein). The circulating miRNAs of the blood can be exploited as a form of liquid biopsy, where miRNAs deliver epigenetic gene expression information from various tissues. From a biological point of view, actively secreted miRNAs in exosomes could be the most

interesting. There are several forms of endocrine tumours, where the preoperative diagnosis of malignancy is difficult, such as adrenal tumours. Our research group has been involved in several studies on tissue and circulating miRNA expression in adrenal tumours.Circulating miRNAs can be determined both from unfractionated whole plasm/serum or from extracellular vesicles. The miRNA yield of whole plasm is higher, but actively secreted miRNAs in exosomes could be more specific. In adrenocortical tumours, we could achieve high specificity and sensitivity of exosomal miR-483-5p for the diagnosis of malignancy. Polymerase chain reaction or next generation sequencing are the best for the analysis of plasma miRNAs. The choice of reference gene in PCR studies is a major debated issue. In the session, the theoretical basis, methodological issues and potential applications of this novel field will be discussed.

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NSA6

Abstract unavailable

Debates

Adrenal venous sampling vs. imaging for primary aldosteronism: beware of the caveats! (*Endorsed by the European Journal of Endocrinology*)

D1.1

Adrenal venous sampling vs imaging for primary aldosteronism

Per Hellman
Sweden.

In the work-up for primary aldosteronism (PA) adrenal venous sampling (AVS) is a corner stone. Although challenged during recent years by means of being insensitive and invasive, it remains the so far only method for lateralization of PA. Indeed, omission of AVS in young patients with a clear adrenal nodule on a CT scan, and development of noninvasive alternatives using positron emission tomography (PET), may replace AVS in certain subgroups. A review of the curent status of AVS will be presented.

DOI: 10.1530/endoabs.56.D1.1

D1.2

Against – Adrenal venous sampling vs. imaging for primary aldosteronism: beware of the caveats!

Jaap Deinum
The Netherlands.

Primary aldosteronism (PA), the most frequent form of secondary hypertension, has two main causes: unilateral aldosterone-producing adenoma (APA) and bilateral adrenocortical hyperplasia. APA has the potential for cure of PA by adrenalectomy. In order to identify an APA guidelines advocate adrenal vein sampling (AVS), a technically demanding and expensive procedure of limited availability and with a controversy-raising variety in protocols. CT-scanning is a cheaper and simpler alternative to AVS but its concordance with AVS is poor. The supposed superiority of AVS over CT for selecting patients for adrenalectomy is mostly based on retrospective studies in which management was only guided by AVS and clinical follow-up was often poor, leading to a high risk of bias. We therefore performed a more appropriate, pragmatic diagnostic randomised trial, SPARTACUS (Subtyping PA: a Randomized Trial Comparing AVS and Computed Tomography Scan) in which we used clinical outcomes to determine the clinical value of AVS and CT in 200 patients with PA. The main finding is that clinical outcome after 1 year follow-up, defined as the intensity of antihypertensive treatment, is similar regardless if AVS or CT is used to guide management. Blood pressure, assessed by ambulatory blood pressure measurement, was identical in both groups. The other secondary outcomes, biochemical cure, quality of life were not significantly different. AVS-based management was much more expensive. Intriguingly the concordance between CT and AVS in the AVS arm was only 50%, suggesting that both tests are imperfect to predict biochemical cure after adrenalectomy. Before we can support or discard AVS or CT for subtyping of PA we need more studies with better design. In this debate I will explore what scientific questions must be answered and which hurdles are to be taken in order to improve diagnostic management in PA.

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Receptor profiling is useful for predicting pituitary therapy (*Endorsed by the European Journal of Endocrinology*)

D2.1

Abstract unavailable.

D2.2

Abstract unavailable.

Subclinical hypothyroidism is a disease

D3.1

FOR – subclinicl hypothyroidism is a disease

Stefano Mariotti
Italy.

Primary subclinical hypothyroidism (SH) is commonly defined by laboratory parameters (TSH above the commonly accepted reference range of about 0.4–4.0 mU/l with normal FT4). This definition does not implies actual thyroid dysfunction, since individual variations of hypothalamic-pituitary feedback set point due to endogenous (genetic, age/gender, NTIS) or exogenous (e.g. drugs) factors may lead to TSH increase in the absence of thyroid disease. Thus, to answer the question of this debate if SH 'is a disease', the first step is to not consider SH any condition of increased TSH and serum FT4 without a complete clinical evaluation and further laboratory (thyroid autoantibody assay) and instrumental (ultrasound) investigations. Moreover, the term "subclinical" is somewhat misleading, since symptoms of mild or very mild thyroid failure may be absent or non-specific, with many cases of "clinical" primary hypothyroidism (increased TSH, low FT4) very difficult to recognize on clinical grounds, especially in the elderly. The term of 'mild' (or very mild) primary hypothyroidism is therefore more appropriate. Thus, when increased TSH is associated with one known cause of thyroid failure (mostly autoimmune thyroiditis, previous thyroid surgery or radiation), there should be no doubt that mild primary hypothyroidism 'is a (thyroid) disease'. A different question is whether this mild disease needs to be treated with levothyroxine (LT4), as clinical/overt hypothyroidism. Arguments in favour to treat mild primary hypothyroidism include the risk of progression to overt thyroid failure, increased cardiovascular risk (dyslipidemia, increased atherosclerosis and ischemic heart disease, hypertension, decreased endothelial function, decreased systolic and diastolic heart function), potential impairment of neuro-psychological fetal development in pregnant women and mood/cognition disorders. Although several short-term intervention studies provide evidence for improvement of several cardiovascular and cognitive parameters, the main argument against treatment is represented by the lack of convincing evidence from prospective controlled trials. However, epidemiological data suggest that mild hypothyroidism may be 'protective' in the elderly. Nevertheless, several retrospective meta-analyses consistently indicate higher cardiovascular risk in subclinical hypothyroid subjects aged <65 yrs, suggesting the need of prospective controlled trials to ascertain whether and to what extent an early therapeutic intervention may be envisaged in younger subjects with mild thyroid failure. In conclusion, if increased serum TSH is the consequence of a primary thyroid pathology, subclinical (mild) hypothyroidism 'is' a disease. The question of whether and when this mild disease deserves treatment is far to be answered.

DOI: 10.1530/endoabs.56.D3.1

D3.2

Abstract unavailable.

AMH as the Primary Marker for Fertility

D4.1

AMH is the primary marker for fertility (Pro)

Didier Dewailly
France.

In women, the anti-Mullerian hormone (AMH) is secreted by the granulosa cells of the growing follicles. Its assay is therefore strongly correlated with the antral follicular count and represents a reliable marker of the ovarian reserve. It also has the advantage of being very reproducible since it has little intra- and inter-cyclic variation. However, it seems to be a good quantitative reflection of the ovarian reserve but not qualitative. This drawback does not make this assay a good predictor of female fertility in the general population. On the other hand, the interest of AMH assay in the context of certain situations at risk or in the management of various pathologies is well established and it can become an indirect marker of female fertility. Indeed, the AMH assay is very useful in screening for situations at risk such as early ovarian insufficiency or polycystic ovary syndrome. Its interest is no longer to prove in assisted reproductive techniques where it is a valuable aid to the choice of techniques, ovarian stimulation protocols and dose of gonadotropins. The AMH assay is also very informative in the follow-up of cancer patients who have required the use of ovario-toxic products or who have undergone mutilating surgeries for the ovaries. In conclusion, although it can not be considered in isolation as a reliable predictor of the chance of pregnancy in women, the AMH assay is one of the essential measures in the management of female fertility.

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D4.2

Debate: AMH as the primary marker for fertility

Joop Laven
The Netherlands.

AMH is a dimeric protein hormone and a member of the TGF-β superfamily. AMH is first expressed in granulosa cells of primary follicles and expression persists in growing follicles up to 6 mm in diameter. In follicle stages beyond 8 mm, AMH expression diminishes and ultimately becomes undetectable once the follicle becomes FSH-dependent1. Its measurement is strongly correlated with antral follicle count and represents a reliable marker of ovarian function. It is reproducible since it has little variation within and between cycles. However AMH assays may display differential results due to pre-analytical proteolysis, conformational changes of the AMH dimer, interfering substances, sample handling, transport and storage conditions, factors underreported in the literature. Finally, there is a urgent need for an international reference standard. Although AMH seems to be a good quantitative reflection of ovarian reserve, it does not assess oocyte quality. This drawback precludes any good prediction of female fertility in any patient population. Although, AMH constitutes a promising marker for age at natural menopause (ANM). As such AMH does not predict the extremes of menopause very well and predicted ages show wide confidence intervals. Hence AMH as a marker for ANM clearly needs improvement before they can be used in the clinical setting. On the contrary AMH assays might become an indirect marker of ovarian function in some women at risk for premature ovarian failure or in the polycystic ovary syndrome. Its interest is no more to be proven in assisted reproductive technology where it is a valuable aid in determining gonadotrophin dosage. AMH is finally very informative in monitoring cancer patients after gonadotoxic drugs or having undergone mutilating ovarian surgeries. In conclusion, although AMH assays are widely used AMH itself is not a reliable predictor of pregnancy in women and therefore it does not predict fertility!

DOI: 10.1530/endoabs.56.D4.2

Pregnant women should be screened for thyroid hormones and antibodies

D5.1

Abstract unavailable.

D5.2

AGAINST: 'Pregnant women should be screened for thyroid hormones and antibodies'

Brigitte Velkeniers & David Unuane
Department of Endocrinology, UZ Brussel, Vrije Universiteit Brussel, Laarbeeklaan, 101 1090 Brussels.

Screening is a process of identifying apparently healthy people at increased risk of a disease or condition. They can then be offered appropriate treatment to reduce the risk arising from the disease or condition.
Thyroid autoimmunity (TAI), defined by the presence of antibodies against thyroperoxidase and thyroglobulin, have been associated with adverse pregnancy outcomes, infertility, and impaired child neurodevelopment. However, associations do not necessarily mean a causal relationship. Other risk factors associated with TAI should be considered, including other organ specific autoimmunity, age, smoking and BMI. Moreover, thyroid autoimmunity can merely reflect an immune dysfunction. TAI is often related to the development of subclinical hypothyroidism during pregnancy, with an inadequate thyroid response to human chorionic gonadotropin. So far, the use of levothyroxine in interventional studies has not provided sufficient evidence to recommend its use in euthyroid TAI pregnant women. It remains unclear whether potential benefits outweigh the possible harm, due to overtreatment during pregnancy. Thyroid hormones (TSH, fT4) are important to sustain pregnancy and neonatal outcome. Clinical thyroid dysfunction (hypothyroidism, hyperthyroidism) should be diagnosed and treated. Subclinical hyperthyroidism has not been associated with adverse pregnancy outcomes. However uncertainty persists with regard to subclinical hypothyroidism. As for TAI, subclinical hypothyroidism has been associated with impaired child neurodevelopment and adverse obstetric outcomes. Intervention studies with levothyroxine in pregnant patients with subclinical hypothyroidism were unable to sustain an improvement in offspring's neuropsychological development. The evidence for intervention with a reduction in adverse obstetric outcomes in this population is weak, with studies lacking adequate power and appropriate design. Also policy on cut-off levels to define TAI and suitable thyroid hormones in pregnancy remains to be determined. Therefore, we recommend against universal screening for TAI and thyroid hormones in pregnant women, but do acknowledge the use of a case finding approach.

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Endocrine disruptors: Regulatory vs. Scientific Perspectives (*Endorsed by Endocrine Connections*)

D6.1

Abstract unavailable.

D6.2

Endocrine disruptors: Regulatory vs. Scientific Perspectives (regulatory view point)

Sharon Munn
Italy.

Societal concerns have been growing with respect to the impact of manufactured chemicals in the environment on human health and wildlife and particularly the link to endocrine-related disorders. The European Commission issued a Community Strategy on endocrine disruptors (EDs) in 1999 to identify the causes and consequences of endocrine disruption and to identify appropriate policy action. The implementation of this strategy has led to a greater understanding of endocrine disruption from EU supported research; identification of priority lists of substances for further investigation with respect to their role in endocrine disruption; the validation and acceptance of OECD test guidelines for the identification of EDs; and the introduction of legislative provisions within chemical control-related legislation. Under the authorisation schemes for pesticides (Reg. (EC) 1107/2009) and biocides (Reg. (EU) 528/2012) criteria were required to be set for the identification of endocrine disruptors. These criteria (adopted for biocides in September 2017 and still undergoing the adoption process for pesticides) are based on the WHO/IPCS definition and can be

considered to consist of 3 main elements requiring evidence for i) endocrine activity, ii) an adverse effect, and iii) a biologically plausible link between elements i) and ii). The drafting of guidance on the implementation of the criteria is now underway by the responsible European Agencies, EFSA and ECHA. This guidance is built on the currently available OECD test guidelines relevant to the investigation of a chemical's potential to interfere with oestrogen, androgen or thyroid hormone action. A systematic review of the scientific literature is also required which could uncover evidence for activity on other endocrine pathways. In order to improve the current suite of regulatory test guidelines the EC is funding activities to identify the gaps and propose solutions to fill the gaps through the multi-disciplinary engagement of relevant experts, particularly within the fields of toxicology and endocrinology.

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Meet the Expert Sessions

MTE1

Using diabetes technologies to improve patient self care

Valeria Alcántara-Aragón
Spain.

Diabetes technologies are evolving rapidly. They offer exciting opportunities to improve patient self-care but they may also be challenging for both patients and health-care providers. Thus, the use of technology may empower or burden. To understand and benefit from the use of these technologies we must first go beyond HbA1c, understand what truly matters to our patients, and what technology can provide in this setting. Available data on the use of technology including insulin pumps, continuous glucose monitoring (CGM), flash monitoring, wearables, web and mobile apps, as well as integrated systems will be reviewed. The review of these technologies will focus on how they may improve patient's safety, self-efficacy, comfort and normalization. The use of these technologies is usually not optimal unless there is appropriate therapeutic education by health-care providers, the key aspects to consider in the process will also be evaluated. Clinical trial results from the use of these technologies are necessary, important and will be the basis of the review; however information and experience from true-life conditions are priceless and what makes a true expert. To provide this valuable perspective, the true-life conditions and diabetes technology expert, Adam Brown will also provide his input on how to use these technologies to improve patient self-care.

DOI: 10.1530/endoabs.56.MTE1

MTE2

Acromegaly: Optimal management after surgery

Michal Krsek
Czech Republic.

Acromegaly is a rare condition caused by overproduction of growth hormone (GH). Early diagnosis, optimal treatment and follow-up is essential for prognosis of patients with acromegaly. Surgery is first choice treatment of acromegaly. Cure rates range around 80% (63–100%) in GH secreting microadenomas, however only about 50% (40–72) in macroadenomas. If not curable, surgery has to be followed by other treatment modalities to achieve treatment goals that are according to Endocrine Society guidelines normalization of age adjusted IGF-I serum levels and random GH levels <1 μg/l. Medical tools for GH secreting adenomas include dopaminergic agonists, somatostatin analogues (SSA) and pegvisomant. Radiotherapeutic techniques include stereotactic radiosurgery and fractionated stereotactic radiotherapy. Cabergoline is effective usually in patients with modest hormonal activity only. In monotherapy normalizes IGF-I levels in approximately 30% of patients. However, it could be useful in combination with other drugs. SSA are probably most frequently employed in therapy of residual disease taking the advantage of combination of antisecretory and antitumoral affects. Hormonal normalization rate of 'classical' SSA, lanretoide and octreotide, is approximately 55%, moreover, they lead to significant shrinkage (>20% volume %) of tumorous tissue in approximately 57% of patients. In patients resistant to classical SSA, multiligand SSA pasireotide can be successfully applied and is effective in biochemical control in about 20% of previously resistant patients. Pasireotide is a GH receptor antagonist able to block GH biological action and decrease IGF-I production. It is effective in most patients in normalizing IGF-I levels depending on the dose used. However, it has no antitumoral affect. Radiotherapy is a third-line therapy according to Endocrine Society guideline. Advantage of radiotherapy is its antitumoral effect enabling to withdraw medical therapy in most patients. Proton beam therapy has recently been used for treatment of acromegaly.

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MTE3

Managing delayed puberty

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Finland.

Delayed puberty (DP) is traditionally defined as the absence of testicular enlargement by the age of 14 years in boys and absence of breast development by 13 years in girls (1). In both sexes, DP is most frequently caused by constitutional delay of growth and puberty (CDGP), which represents a late variant of the normal timing of puberty (1-3). Other possible causes for DP include permanent hypogonadotropic hypogonadism (HH), functional hypogonadotropic hypogonadism and hypergonadotropic hypogonadism due to gonadal failure. Differential diagnosis of DP can be sometimes challenging, and especially, differentiating between CDGP and partial congenital HH can be notoriously difficult, if not impossible. In our recent analysis of a large patient series from a single academic center, we described the etiology of DP in 174 boys and 70 girls, identified prognostic markers to help the diagnostic procedure, and investigated the relationship between linear growth and different etiologies of DP (3). In this case-based session, we will briefly review the basic concepts of puberty, consider different aspects of the diagnostic procedure in patients with DP in the light of this data, review the treatment options, and discuss the importance of accurate and timely diagnosis.

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MTE4

Osteoporosis in men: management of bone health in the endocrine outpatient clinic

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Belgium.

Several wrong conceptions persits with respect to male osteoporosis which unfortunately lead to under- diagnosis as well as under- treatment of this disease. Osteoporosis is still considered a female disorder. However, osteoporosis is not a rare condition especially in elderly and/or hypogonadal men. Moreover, fractures in elderly men are even more strongly associated with mortality than in women. Most of the risk factors for osteoporosis are also similar in men compared to women. These risk factors are easily identified but remain still insufficiently recognized. Dual energy dual energy absorptiometry is also a useful additional tool for the diagnosis of male as well as postmenopausal osteoporosis despites gender differences in bone structure. Reduction of fracture risk as result of antiresorptive as well anabolic anti-osteoporotic therapy is less well established in men than in postmenopausal women. Available data however indicate the outcome of anti-osteoporotic treatment in men at high risk for osteoporosis is not different from women. Therefore, current therapeutic lethargy in men at risk of fractures is not justified. The efficacy of testosterone supplementation with respect to prevention and treatment of osteoporosis however is less well documented in these men. In this lecture a practical approach for management of men with low and borderline low testosterone levels will therefore be presented with specific reference to a recent guideline on this topic of the European academy of andrology.

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MTE5

Medullary thyroid cancer beyond surgery

Ana Luiza Maia
Brazil.

Medullary thyroid carcinoma (MTC) is a rare thyroid C cell malignant tumor that accounts for 3-4% of thyroid gland neoplasias. MTC may occur sporadically or be inherited. Hereditary MTC appears as part of the MEN 2 syndrome. Germ-line mutations of the RET proto-oncogene cause hereditary cancer, whereas somatic

mutations are frequently present in sporadic disease. Currently, early MTC diagnosis followed by total thyroidectomy offers the only possibility of the cure of the disease. Although the majority of MTC patients have a good prognosis, a subgroup of patients develops progressive disease and requires systemic therapy. We will focus on the current therapeutic approaches for patients with advanced disease discussing the advantages and disadvantages of molecular targeted therapies that inhibit RET and other tyrosine kinase receptors involved in tumor angiogenesis. Treatment with tyrosine kinase inhibitors (TKI) increases the progression-free survival but we still needed to answer the question of whether it impacts on overall survival. Hopefully, the cumulative knowledge about molecular profiling of MTC and the TKI-associated side effects will help in choosing the best therapeutic approach to enhance their benefits.

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MTE6

Long-term implications of hypoglycaemia in diabetes Dr Ilhan Satman, Istanbul University, Turkey

Ilhan Satman
Turkey.

Hypoglycaemia is associated with considerable morbidity and even mortality in type 1, and less likely in type 2 diabetes. Generally, hypoglycaemia is accepted as a surrogate marker of poor health as it is likely to be more prevalent in renal and liver failures, which independently increase cardiovascular diasease (CVD) and neurocognitive risks. Hypoglycaemia, have been implicated with a fortunately rare but tragic event, 'dead-in-bed' syndrome. It has been hypothesised that nocturnal hypoglycaemia can lead to the dead-in-bed syndrome via its pro-arrhythmogenic effects. Hypopglycaemia, due to its effects on inflammation and thrombosis can increase CV risk in both types of diabetes. In addition to adverse biological effects, repeated hypoglycaemias has been shown to significantly impair quality of life, and leading to depression in older people with diabetes. Negative psychological effects of hypoglycaemia are particularly deleterious as they can establish a cognitive barrier preventing treatment of future episodes and thus interfering the treatment of hypoglycemia-associated autonomic failure (HAAF). Hypoglycaemia has a significant impact on the risk of fall and related injuries, and dementia or cognitive impairment by various mechanisms. Hypoglycaemia is a major limiting factor for optimising glycaemic control, especially in patients with long-duration type 1, as well as in older patients with type 2 diabetes. Impaired renal and hepatic metabolism with slower counter-regulatory mechanisms, polypharmacy or non-adherence to medications, as well as erratic or poor food intake are the key components of hypoglycaemia in older individuals. Simply relaxing HbA1c goals may reduce the risk but it is not sufficient to protect frail older people against hypoglycaemia. These people may benefit from a switch to regimens including anti-hyperglycaemic drugs that do not induce hypoglycaemia. In conclusion, hypoglycaemia remains a real and continuing problem for people with diabetes. Developing strategies, technologies, and/or therapies designed to prevent and/or minimize the risk of hypoglycaemia is utmost important.

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MTE7

Difficult cases of differentiated thyroid cancer

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Hungary.

The incidence of differentiated thyroid cancer (DTC) has increased worldwide which is mainly attributed to the more common detection of early stage DTC. The prognosis of early stage disease is excellent and the present ATA guidelines suggest less radical treatment and follow-up in these cases. TNM staging, risk classification, indication of radioiodine (RAI) treatment, evaluation of therapeutic response and TSH target range have been recently changed. However, 7–10% of DTC cases develop distant metastases and two-thirds of these patients become RAI-refractory. The management of RAI-refractory patients has markedly developed with the availability of new treatment modalities. The presented cases represent the major challenges during the risk classification, follow-up, treatment of choice and emphasize unresolved questions. The patient with papillary thyroid cancer (PTC) is tumor-free after the primary treatment (surgery and RAI) but rising anti-Tg antibody levels are found in the absence of localizable disease – biochemical incomplete response. Anti-Tg antibody positive PTC patient with rising antibody levels and development of lymph node and RAI-refractory pulmonary metastases 9 years after the diagnosis – percutaneous ethanol sclerotherapy (PEI) of lymph node metastasis. The patient tolerated sorafenib treatment only temporarily due to severe side effects. Young PTC patient diagnosed with advanced disease (pT4N1M1), pulmonary metastases and treated with repeated surgeries including gamma-probe guided operation and five RAI therapies. He is followed for 12 years. When can we stop the RAI therapy? A PTC patient with 30-years disease course who underwent five surgeries, five RAI therapies and PEI of recurrent neck lymph node metastases and suspected tongue metastasis and finally PET/CT detected non-RAI avid lymph node mets in the upper mediastinum. A patient suffering from oncocytic follicular cancer, local relapse, cervical lymph node and pulmonary metastases; 17-years disease duration, 3 surgeries, 3 RAI therapies, 2 irradiations and sorafenib therapy since 2012; successful reintroduction of sorafenib treatment after the surgery of metastatic cervical lymph nodes with rapid progression.

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MTE8

Hormone replacement for the travelling patient

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Croatia.

Millions of people travel across time zones every day for business and for pleasure. Travel-related health issues arise from a variety of factors: infections, prolonged limited mobility during travel, and participation in certain activities, such as diving and high-altitude hiking during travel. Besides that, air travel allows individuals to traverse time zones faster than the internal clock, or circadian rhythm, can adjust. This results in desynchrony between the external light-dark cycle and the endogenous circadian rhythm. Adjusting the hormone replacement during travel in people with endocrine dysfunctions can be challenging. Adjusting strategies vary depending on the medication, the importance of precise timing of medication usage, distance travelled, and duration of the visit. In general, in patients with diabetes, adjustments of insulin doses are unnecessary if patients are crossing fewer than five time zones. Traveling east will shorten one's day, and, in general, may require a reduction in insulin because insulin doses would be administered closer than normal and thus could cause hypoglycemia. Westward travel means a longer day, and so insulin doses may need to be increased. People with adrenal insufficiency should switch the hydrocortisone schedule to the local time. Throughout the time of travelling, hydrocortisone should be used every five to six hours. Estrogen use represents a risk factors for the development of venous thromboembolism during long-distance travel and therefore, in women taking estrogens, prevention of venous thromboembolism during prolonged travel should be considered. Continuous patient education regarding hormone replacement and prevention of possible acute complications are the cornerstones of managing common travel-related problems in patients with endocrine disorders.

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MTE9

Premature ovarian insufficiency: an endocrine perspective

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Serbia.

Premature ovarian insufficiency (POI) is defined as hypergonadotropic oligo/amenorrhoea with FSH $>$ 40 IU/l, estradiol $<$ 50 pmol/l in women under 40 years of age. Biological aging is faster in this group of women inducing diseases and disturbing quality of life.Infertility in POI represents a special issue. Hypoestrogenism, hypoprogesteronism, hypoandrogenism, decreasing of dehydroepiandrosteron sulfate, growth hormone, and increasing insulin resistance influence all body functions knowing the fact that steroid receptors are present on all blood vessels.Central nervous system changes include depression, lack of concentration, insomnia, anxiety, lower sexual desire and increasing incidence of Alzheimer disease. Cardiovascular changes include blood vessel instability, hypertension, atherosclerotic plaque growth, myocardial infarction, arrhythmias etc. Insulin resistance increases body weight further contributing to

cardiovascular disease. Osteoporosis, joint stiffnes, cartilage and connective tissue changes restricted mobility. Inflammation increase and autoimmune diseases started at that time. Dyspareunia, vulvar atrophy, lower libido ruined sexual life. All these consequences of 'normal aging and physiological menopause process' are not acceptable today having in mind definition of middle age until 60 years of age, according to World Health Organization. The main principle of endocrinology is to reach normal hormone concentrations. In POI estradiol has to be not only sufficient but optimal, according to the age. Adequate replacement of estradiol, progesterone, testosterone (especcialy in the artificial POI), DHEAS and all other hormones is required in POI. Modern endocrinology is responsible for helping women in reaching the optimal quality of life which is impossible without normal gonadal steroids levels.

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MTE10

The effect of gender-affirming therapy on bone in transgender persons

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Belgium.

Transgender persons on gender-affirming hormonal therapy will have experienced a hormonal reversal that will have had direct and also indirect effects on bone, through body composition changes. Recent evidence suggests that transgender women, even before the start of any hormonal intervention, already have a lower bone mass including a higher frequency of osteoporosis, and a smaller bone size vs. cisgender men. During gender-affirming hormonal treatment, bone mass is maintained or increased in transgender women. In transgender men, bone metabolism seemed to increase during short-term testosterone therapy, but no major changes have been found in bone density. On long-term testosterone therapy, larger cortical bone size was observed in transgender men vs. cisgender women. Fracture data as hard endpoint are not available currently. The follow-up of bone health and osteoporosis prevention in transgender persons is important, especially in transgender women. We advise active assessment of osteoporosis risk factors including the (previous) use of hormonal therapy. Based on this risk profile and the intended therapy, bone densitometry may be indicated. Long-term use of antiandrogens or gonadotropin-releasing hormone agonists alone should be monitored as transgender women may have low bone mass, even prior to treatment. Therapy compliance with the gender affirming hormones is of major concern, especially after gonadectomy. Large-scaled, multicenter, and long-term research is needed to determine a well tolerated dosage of gender-affirming hormonal treatment, avoiding side effects. Data on gender non-binary persons and elderly transgender persons are lacking altogether.

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MTE11

How to integrate PCSK9 inhibitors into hyperlipidemia management

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Romania.

Anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies are a new class of biological drugs that inhibit binding of PCSK9 to the LDL receptor, thus increasing LDL-receptor density and lowering circulating LDL-cholesterol (LDL-C), apo-B100 and Lp(a). Recently released guidelines on management of hyperlipidemia reinforced the attribute of statins as the mainstay of lipid-lowering medication in dyslipidemic at-risk individuals, as every 1.0 mmol/L reduction in LDL-C is associated with a corresponding 20–25% reduction in cardiovascular disease mortality and non-fatal myocardial infarction, in addition to non-LDL-C benefits. Clinical trials demonstrated the advantages of treating extreme risk patients to an LDL-C target $<$55mg/dl by high-intensity statin or add-on non-statin therapies; statin and ezetimibe or, based on outcomes from FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) and ODYSEEY clinical program and particularly when $>$25% additional lowering of LDL-C is required, the combination treatment of statin and PCSK9 inhibitors is suggested to accomplish lipid and cardiovascular goals in patients with or without diabetes. PCKS9 inhibitors are capable of further decreasing LDL-C to around 60% when added to maximum statin therapy, which translates for evolocumab into 1% reduction in atheroma volume and atheroma plaque regression in about two-thirds of patients. Therapeutic challenges posed by genetic, familial heterozygous or homozygous hypercholesterolemia might be overcome by adding to maximally tolerated statin therapy non-statin agents including PCSK9 inhibitors, although homozygous receptor negative hypercholesterolemia patients may not respond. As a class effect, PCSK9 inhibitors address dyslipidemia in statin intolerant patients, with evolocumab being slightly more effective compared to ezetimibe in terms of LDL-C reduction and with an overall good tolerability. Adverse effects ($<$2–5%) commonly include nasopharyngitis, muscle-related events, back and leg pain, arthralgia, headache. Conclusion: PCSK9 inhibitors represent a promising non-statin tool in lipid management to be considered in well-defined clinical circumstances.

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MTE12

Controversies in NETs: Is high dose SSA treatment relevant and who needs hemicolectomy?

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Greece.

Long-acting somatostatin analogs (SSAs) have long been used for symptom control in patients with functional neuroendocrine tumors (NETs) whereas two recent prospective studies (PROMID and CLARINET) have demonstrated their efficacy in controlling tumor growth in patients with gastrointestinal NETs of different tissue origin. For both purposes currently available agents (octreotide LAR 10–30 mg i.m and lanreotide autogel 60–120 mg s.c.) have been used. In case of refractory syndromes dose escalation or shortening the injection interval form 4 to 3 or 2 weeks has been used. There is agreement that dose escalation is justified in patients with refractory carcinoid syndrome for symptom improvement and potentially the prevention of carcinoid heart disease. Long-acting SSAs have also been used in a non-prospective manner at above the upper labeled dosages for obtaining tumor growth control. The efficacy of high dose octreotide-LAR has been reported in 10 studies. Doses studied ranged from a minimum of either 40 mg per month or 30 mg per 3 wk up to a maximum of 120 mg per month and included over 260 patients. Eight studies suggested that increased doses (median 60 mg/day) could be effective at preventing tumor growth without evidence of increased toxicity. A prospective study is currently evaluating whether Lanreotide Autogel 120 mg given twice monthly may exert further tumor control in patients with established progression on 120 mg/monthly. Appendiceal carcinoids are considered to be amongst the most indolent carcinoid tumors with only a minority developing metastatic disease. As the majority of patients are identified incidentally when undergoing an appendicectomy a number of potentially adverse histopathological findings have been employed to identify patients that may require a hemicolectomy to eradicate any residual disease. Although there is relatively lack of good quality data, tumor size and grade seem to be the ones with the highest predictive value.

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MTE13

Erectile dysfunction

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Italy.

Erectile dysfunction (ED) is a multidimensional disorder characterized by the inability to have successful intercourse with negative consequences in personal self-esteem and in couple relationship. Organic, relational and intrapsychic problems always concur in determining the erectile problem, although in different combination according to the patient characteristics, including age. Fifteen years ago, we have developed and validated a structured interview to identify and quantify the weight of each ED determinant. The organic determinant contributes significantly to ED in all age bands. In young and middle-age patients, intrapsychic disturbances are also important, while they result no longer statistically significant in aged individuals. Relational problems show a major contribution in younger subjects. Recognizing and treating ED is important in all age bands, because they often represent a harbinger of forthcoming cardiovascular (CV) problems. This is particularly relevant in young individuals, where having ED strongly increase CV risk. Several endocrine disorders are underlying the

organic component of ED. Among them are metabolic disturbances, such as diabetes mellitus (T2DM) and obesity, hypogonadism, hyperprolactinemia and, to a lower extent, thyroid diseases. Recognizing the underlying endocrine disorder is of capital relevance because treating it could restore a normal erectile function and improve overall health. For example, treating hypogonadism significantly improve erectile function, as demonstrated by a recent meta-analysis considering RCTs having International Index of Erectile Function (IIEF) as endpoint. However, the improvement in IIEF score was modest upon testosterone replacement therapy (TRT), i.e. 2–3 points, and apparent only in trials involving overt hypogonadism. Hence, there is often the need to associate other types of intervention to fully restore erectile function. Considering that T2DM, obesity and metabolic syndrome (MetS) are the major cause of ED-associated hypogonadism, their treatment is mandatory for sexual health. In fact, lifestyle intervention, including physical activity, improves erectile function and often reverts hypogonadism. In an experimental model of MetS we demonstrated that in the hypothalamus there is clear inflammation associated to a decrease in GnRH expression, secondary hypogonadism and ED. In MetS rabbits, regular physical activity (treadmill) reverted hypothalamic alterations, doubling GnRH expression, restoring normal testosterone levels and erectile function, including cGMP signaling within the penis. Several medications blocking cGMP catabolism in the penis, through the inhibition of phosphodiesterase type 5 (PDE5 inhibitors), are available as a symptomatic aid for improving ED. Although PDE5 inhibitors result very efficient in improving ED (more than 5 IIEF points) they do not resolve the underlying problems.

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MTE14

Vitamin D for everybody?

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Austria.

Vitamin D deficiency has a high worldwide prevalence. This is of concern for public health because a poor vitamin D status can lead to musculoskeletal diseases such as rickets and osteomalacia, but vitamin D may also prevent extraskeletal diseases such as respiratory tract infections and reduce premature deaths. Several nutritional guidelines have been revised within the last few years leading to and increase of the recommended dietary reference intakes for vitamin D. Based on a consensus that serum 25-hydroxyvitamin D (25[OH]D) concentrations are used to assess vitamin D status, the recommended target levels for 25(OH)D usually range from $\geq$ 25 to 50 nmol/l (10–20 ng/ml), corresponding to a daily vitamin D intake of 400–800 international units (10–20 μg). General populations clearly fail to meet these recommended dietary vitamin D requirements. In Europe, 25(OH)D concentrations $<$30 and $<$50 nmol/l are present in 13.0% and 40.4% of the general population, respectively. This definitely requires action from public health authorities. Approaches to increase vitamin D status include promotion of a healthier lifestyle, vitamin D supplementation or vitamin D food fortification. The current knowledge on vitamin D safety provides a solid basis to introduce vitamin D food fortification in order to improve public health with this very safe and cost-effective approach. On the other hand, we also have to deal with vitamin D diagnostics and treatment in patient care that is challenging due to inconsistent recommendations and several knowledge gaps regarding clinical effects of vitamin D supplementation.

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MTE15

Your emergency consult about hyponatraemia

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UK.

Hyponatraemia is the commonest electrolyte disturbance in hospital patients. It may be observed in up to 30% of cases and it has been clearly associated with an increased morbidity and mortality in a diverse array of clinical scenarios. Despite the frequency of the problem, robust evidence examining its importance and comparing treatment options has traditionally been lacking. However, recent years have seen the publication of high-quality prospective studies evaluating the epidemiology, clinical importance and management of hyponatraemia. Several clinical practice guidelines for the assessment and management of hyponatraemia have been published. However, hyponatraemia is encountered in such a broad spectrum of patients, often with complex comorbidities, that a physician's judgement and individualised management are still required in everyday clinical practice. The commonest cause of hyponatraemia in hospital is the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). However, glucocorticoid deficiency can mimic this syndrome, accounting for up to 4% of cases originally diagnosed as SIADH. Fluid restriction has been the mainstay of treatment for SIADH for many decades. The safety and efficacy of this treatment has not been rigorously examined in prospective trials. Furthermore, it can be practically difficult to implement and maintain in hospital patients. Recently, following the publication of prospective, randomised controlled trials, vasopressin receptor antagonists have been approved for the treatment of SIADH. Clinical experience with these agents is growing worldwide. Severe symptomatic hyponatraemia is particularly challenging. It requires urgent, careful management, with frequent monitoring of serum sodium, to reduce the risk of mortality and avoid permanent neurological injury. This interactive clinical session will discuss cases of hyponatraemia in hospital patients to illustrate complexities in management and suggest approaches to assessment and treatment.

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MTE16

Adrenal Incidentaloma

John Newell-Price
UK.

An adrenal incidentaloma is a mass in the adrenal gland that is found on imaging that has been performed for reasons other than imaging the adrenal. With the increased use of axial imaging increasing numbers of lesions are found that require assessment. Adrenal incidentaloma are found in 4.5% of abdominal and thoracic CT scans. The incidence increases with age, being found in $<$1% of scans in those aged $<$20 y but in around 10% at 70 y. These adrenal masses are encountered by all medical and surgical specialities during radiological investigation. Large retrospective series reveal that the vast majority of adrenal incidentaloma are benign adrenal cortical adenoma, but a wide range of other diagnoses are possible depending on whether there is unilateral or bilateral disease. The two key questions that need to be addressed when assessing an adrenal incidentaloma are: 1) is it benign or malignant? 2) is it functional? These key questions are best addressed by discussion in dedicated adrenal multi-disciplinary team (MDT) meetings attended by specialists expert in assessment of adrenal disease including: adrenal radiologist, adrenal endocrinologist, endocrine / adrenal surgeon, oncologist, clinical chemist, and endocrine nurse specialist. This MTP session will focus on case-based analyses and examples of how to approach this common clinical problem with extensive reference to the European guidelines.

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MTBS1

Abstract unavailable

MTBS2

Single-cell technologies in development and disease with a special emphasis on endocrine systems

Karine Rizzoti
London.

Recently developed single cell technologies offer unprecedented investigations of cellular heterogeneity. While significant hurdles remain to be overcome, the field is progressing rapidly. In addition to now commonly performed genome and transcriptome analysis, it appears possible to examine the epigenome, proteome and metabolome at the single cell level. In addition, multi-omics technologies are being developed to profile simultaneously different material sources from the

same cell, enabling for example correlations between genomic mutations and alteration of genes expression. Genome and transcriptome analyses were initially pricey and required wet-lab specialist skills. However, competitive sequencing costs, commercially available kits for material preparation, along with the development of techniques to extract good quality material from clinical samples render these analyses more accessible to both biomedical and clinical researchers. Nevertheless, specialist platforms for microfluidic or droplet technologies are often required, and specialised bioinformatic support is essential for quality control and data analysis. Single cell analyses have already provided significant advances, in particular in the field of cancer, and stem cell research. In contrast with bulk population analysis, examination of genomic material from tumour single cells reveals cellular heterogeneity, allow reconstitution of cellular hierarchies, and sometimes resolution to the cell(s) of origin of the tumour. This maybe the only way to identify rare cell types, and therefore better characterize mechanisms of resistance to treatments, and tumour reoccurrence. In addition, stromal niche cells can be segregated away from tumour cells, and their analysis offer clues to understand how the microenvironment interact with the tumour cells. Furthermore, characterisation of circulating (CTC) and disseminated (DTC) tumour cells can be performed. In stem cell research, characterisation of differentiation pathways is a central question to improve disease modelling and drug screening assays, and ultimately for regenerative medicine. Single cell transcriptome analysis coupled with the development of specific algorithms allows pseudotime analysis of heterogeneous cellular states, and reconstitution of differentiation pathways, with often characterisation of new, previously invisible, intermediate cell states. A special emphasis will be placed to exemplify the advances these technologies have provided in endocrine systems, in both normal and pathological situations. Finally, current challenges and future developments of these techniques will be discussed.

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MTBS3

Watch out for noncanonical mechanisms of thyroid hormone action!

Lars Moeller
Germany.

Thyroid hormone (TH) and TH receptors (TRs) α and β act by binding to TH response elements (TREs) in regulatory regions of target genes. This nuclear signaling is established as the canonical or type 1 pathway for TH action. Nevertheless, TRs also rapidly activate intracellular second-messenger signaling pathways independently of gene expression (noncanonical or type 3 TR signaling). To test the physiological relevance of noncanonical TR signaling, we generated knockin mice with a mutation in the TR DNA-binding domain that abrogates binding to DNA and leads to complete loss of canonical TH action. We show that several important physiological TH effects are preserved despite the disruption of DNA binding of TRα and TRβ, most notably heart rate, body temperature, blood glucose, and triglyceride concentration, all of which were regulated by noncanonical TR signaling. Additionally, we confirm that TRE-binding-defective TRβ leads to disruption of the hypothalamic–pituitary–thyroid axis with resistance to TH, while mutation of TRα causes a severe delay in skeletal development, thus demonstrating tissue and TR isoform-specific canonical signaling. These findings provide in vivo evidence that noncanonical TR signaling exerts physiologically important cardiometabolic effects that are distinct from canonical actions. These data challenge the current paradigm that *in vivo* physiological TH action is mediated exclusively via regulation of gene transcription at the nuclear level.

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Nurse Sessions

N1.1

Abstract unavailable.

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N3.1

Nursing Management of Congenital Adrenal Hyperplasia (CAH): - Education, Managment and use of Multi-Media Technology

Irene Mitchelhill
Australia.

Introduction
The management of Congenital Adrenal Hyperplasia (CAH) requires specific expertise and understanding in childhood, adolescence and adulthood. Patient education and support is an integral part of this health care process, from the delivery of a diagnosis and explanation by medical staff to the more detailed education provided by nurses in order to help families understand the practical aspects of management.
Background
For parents, the initial diagnosis of CAH is an extremely traumatic time and the grief experienced significantly affects the parental learning process. The appearance of atypical genitalia in a newborn female, or the near death experience of an extremely unwell male infant is a devastating experience for the parents, and the beginning of a long road ahead. Parents need to come to terms with the implications of an autosomal recessive condition, its life-threatening nature, and need for life-long treatment and management. At this time the nurse-patient relationship is crucial in providing emotional support and explanation to support the parents through their grief process. Recognition of specific illness stressors (emotional, cognitive, practical) affecting any learning process needs to be addressed in order to support parental ability to cope and understand. The endocrine nurse role is to provide pschosocial support, education and advocacy. Evaluation and management of the emotional needs of the parents and the clinical needs of the child is an essential component. Providing education initally for parents and child as they grow through adolescence to adulthoodand is ongoing, at the same time continually supporting the parents about their long-term fears for their child's future in adult life.
Conclusion
With CAH primarily a childhood condition, transition to adult care can have its challenges. Health education long term and overall the management plans for CAH should focus on minimising the long-term consequences of over treatment with cortico-steroids in order to suppress the effects of the excess androgen secretion and to ensure a positive wellbeing for adults. Finding the balance is challenging physically and emotionally and can be frustrating for patients. Health Education is now being challenged by public access to information on the internet. Our concern about the validity of such information and its interpretation led to the development of a comprehensive and validated psychococial education program (CAHPEP) for families and patients with CAH, is now a website titled 'CAHPepTalk.com', with translations in Vietmamese, Bahasa-Indonesian and Urdu-Pakistan, with the support of Caring Living As Neighbours (CLAN), APPES & APEG.

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N4.1

Abstract unavailable.

N4.2

Abstract unavailable.

N4.3

Comparison of glucose, peak growth hormone & peak cortisol levels during insulin tolerance testing with two different doses (0.15 vs 0.10 U/kg)

Phillip Yeoh
UK.

The Insulin Tolerance Test (ITT) is the gold standard test to assess growth hormone (GH) and ACTH reserve. This dynamic test induces hypoglycaemia and is commonly performed by endocrine nurses using different insulin doses - commonly 0.15 U or 0.10 U/kg. As part of a quality and safety improvement initiative we conducted a retrospective study to address several questions relating to ITT insulin dose. ITT results ($n = 148$) were retrieved from two large endocrine testing centres. All tests that achieved adequate hypoglycaemia on 1st insulin dose and non-diabetic patients. All patients were given glucose after achieving hypoglycaemia at 30 mins.

Results

- Both insulin doses appear to achieve adequate hypoglycaemia
- Patient glucose levels appear to recover more quickly with the lower dose – thus an important patient safety aspect
- Peak GH levels were similar between insulin doses
- Patients receiving the standard (0.15 U/kg) dose were more likely to exhibit an adequate cortisol response, this might be due to the enhanced stimulus from longer hypoglycaemia although we cannot exclude that this is due to possible patient differences as this is not a truly random sample.

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N4.4

Cooperation between an endocrine nurse, psychologist and physician and their role in the care of depression in patients treated with multi kinase inhibitors due thyroid cancer

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The treatment with multi kinase inhibitors (MKI) under clinical trials due to advanced thyroid cancer (TC) may postpone moving on the patients with advanced disease to the palliative care stage. However, chronic and escalating somatic symptoms during the treatment may promote the appearance of depressive reactions. It can be expected that a cognitive image of the disease, as a collection of subjective beliefs concerning patient's own illness and treatment, will be an important determinant of mental functioning. The aim of the study was to define a mutual dependence between the intensity of somatic problems, self-image of the illness and depression in patients receiving an experimental treatment of TC.

Material and methods

The study included 32 patients treated with MKI due to TC for at least one year. The study was cross-sectional and it based on different questionnaires: List of Somatic Problems, Beck's Depression Inventory and Short Questionnaire of Diseases Perception (B-IPQ).

Results

Nineteen patients showed severe somatic symptoms (HSS; High Somatic Symptoms), whereas 13 patiens demonstrated none or mild physical symptoms (LSS; Low Somatic Symptoms). The depression intensity was higher in HSS patients than in LSS group. In HSS group a mediating role of self-image relationship to disease somatic symptoms and depression was noticed. The direct effect of somatic symptoms on depression severity was insignificant. While, the belief about a negative impact of physical symptoms on the daily functioning was an important mediator of relations between somatic symptoms and depression in the study group.

Conclusions

The inclusion of interaction aimed at changing the perception of a negative impact of the disease and its treatment on daily life in TC patients can reduce the risk of deterioration in depressive symptoms. The role of a nurse in psychologist-physician-nurse team is crucial for better patients care and quality of life.

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N4.5

Abstract unavailable.

Oral Communications

Benign thyroid diseases

OC1.1

Familial gestational hyperthyroidism caused by Val597ile mutant of TSH receptor gene with human chorionic gonadotropin hypersensitivity

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Context
Familial gestational hyperthyroidism caused by mutations of TSH receptor gene, hypersensitive to hCG, is rare. Only two mutations at the same amino acid (lys183Arg, Lys183Asn) in the leucine-rich region of the extracellular N-terminal domain of the TSH receptor have been reported.
Patients
A 38-year-old woman was seen during the first trimester of her second pregnancy for weight loss (5 kgs), nausea and vomiting. Thyroid function test revealed thyrotoxicosis with increased $fT_3 = 8.3$ ng/dl (2.4–4.1 ng/dl) and free $T_4 =$ 2.3 ng/dl (0.8–1.3 ng/dl) concentrations and low TSH (<0.03 mU/l) levels without anti-TSH receptor antibody. Thyroid ultrasound showed a normal-sized thyroid gland with diffuse hyper-vascularization. Thyrotoxicosis persisted at 2nd trimester ($fT_3 = 7.0$ ng/dl, $fT_4 = 1.3$ ng/dl) and improved spontaneously during the 3rd trimester ($T_3 = 3.5$ ng/dl, $fT_4 = 1.3$ ng/dl). She gave birth to a girl (3300 gr, 48 cm). Interestingly she presented similar symptoms with a loss of 6 kgs during the first trimester of her first pregnancy with low TSH and normal fT_3 and fT_4 levels. Her mother had two children and reported similar symptoms during her first pregnancy. At the age of 66 years, she had normal thyroid function (TSH = 0.92 mU/l) and high gonadotropin (LH = 26.8 IU/l, FSH = 85.7 IU/l) levels.
Results
DNA sequencing of this woman and her mother, led to identify a heterozygous variant (c.1789 G > A) changing Valine to Isoleucine residue at codon 597 in the exon 10 of the TSH receptor. Functional studies of this mutant receptor showed high constitutive activity in regard to the basal level of cAMP and IP3 production (2 to 2.5-fold higher) while responses to TSH were reduced compared to that of wild type receptor (average 50%), and related to low cell surface expression (28% of the wild type receptor). This Val597Ile mutant presented a dose-dependent increase in cAMP in response to chorionic gonadotrophin and luteinizing hormone whereas the wild type receptor was insensitive to those hormones except at high concentration of chorionic gonodotrophin.
Conclusion
We describe familial gestational hyperthyroidism due to a new variant in TSH receptor gene with hCG hypersensitivity. This amino-acid, located in the 5th transmenbrane helix of the receptor, is highly conserved among the receptors for TSH and LH in different species. We analyzed clinical and hormonal data related to the increased constitutive activity of the Val507Ile receptor and thyroid hypersentivity to HCG and LH in women of this family.

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OC1.2

Relationship between TSH values in the first trimester of pregnancy and obstetric and neonatal complications

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Introduction
In recent years, numerous studies on the relationship between the TSH of the first trimester of pregnancy and obstetric complications have been published, and in this context it has been recommended to treat with levothyroxine from certain values of TSH. The aim of this study was to determine the incidence of obstetric and neonatal complications in pregnancies with normal TSH (0.14 to 2.49 mcU/ml) as a basis for assessing complications in pregnancies with TSH between 2.5 and 4.9 mcU/ ml, both treated as not treated with levothyroxine.
Material and methods
Prospective and cohort study of 1184 pregnant women with TSH in between 0.14 and 4.9 mcU / ml in prenatal screening. Groups A were established: pregnancies with TSH 0.14–2.49 (903) and B: pregnancies with TSH 2.5–4.9 (281). Group B was divided by randomization into two subgroups: B1: no treatment with levothyroxine (146), and B2: treatment with levothyroxine (135). The variables spontaneous abortion, induced delivery, caesarean section, weight of the newborn and admission in neonates were collected and a descriptive and analytical analysis was performed with SPSS 19.0.
Results
There were no significant differences in the percentage of abortions between group A (2.7%), and groups B1 (4.8%), and B2 (4.4%). The percentage of deliveries induced in group A (12.7%) was significantly lower ($P<0.001$) than those of group B1 (39.0%), and group B2 (39.3%). The percentage of caesarean sections in group A (7.8%) were significantly lower ($P<0.001$) than those in group B1 (28.8%), and group B2 (23.0%). There were no significant differences in the weights of the newborns of group A (3186 ± 515 gr), B1 (3229 ± 460 gr), and B2 (3187 ± 449 gr) or in gestational age being in the group A of 38.7 weeks ± 2.7; B1 38.5 ± 5.28 and B2 38.42 ± 5. The mean age of pregnant women in group A was 33 years ± 5.04, B1 31.95 ± 5.22 and B2 31.95 ± 5.58. There was no significant difference in neonatal admissions between group A (8.9%) and B1 (11.0%). The percentage of admissions in neonates in group B2 (20.0%) was significantly higher ($P<0.05$) than in B1.
Conclusion
In pregnant women with TSH < 2.5 mcU / ml in the first trimester there are fewer induced births and caesarean sections than in women with TSH between 2.5 and 4.9 mcU/ml. The treatment with levothyroxine from week twelve does not modify this difference.

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OC1.3

Thyroid hormone replacement therapy for subclinical hypothyroidism in adults: systematic review and meta-analysis of randomized-controlled trials

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Introduction
Although widely prescribed, the benefit of thyroid hormone replacement in subclinical hypothyroidism (SHypo) is unclear. We performed a systematic review and meta-analysis of randomized controlled trails (RCTs) to assess the impact of thyroid hormone therapy on clinical outcomes.
Methods
We followed the PRISMA guidelines and registered the study protocol on PROSPERO (CRD42017055536). We searched PubMed, Embase, Web of Science, COCHRANE Library, CENTRAL, Emcare and Academic Search Premier in April 2017. We included RCTs that assessed the impact of thyroid hormone replacement compared to placebo/no intervention in non-pregnant adults with SHypo. Data and bias-risk of included studies were extracted by two independent reviewers. Outcomes were quality of life, symptoms of depression, cognitive function, blood pressure, and the body mass index. We transformed differences in clinical scores (e.g. cognitive function) into standardized mean differences (SMD, positive values indicate levothyroxine benefit) and applied random-effects models.
Results
Overall, 19 of 2,793 initially identified studies met the inclusion criteria, with a total of 2,061 adults randomized. Levothyroxine lowered TSH into reference range in all studies, but showed no benefit regarding quality of life (five studies, SMD −0.03, 95%CI −0.10 to 0.04, I^2 21%), symptoms of depression (three studies, SMD −0.14, 95%CI −0.41 to 0.12, I^2 0%), and cognitive function (four studies, SMD 0.11, 95%CI −0.09 to 0.32, I^2 53%). Seven studies analysed blood pressure and found no clear benefit of levothyroxine therapy compared to placebo (−0.66 mmHg, 95%CI −2.46 to 1.14 mmHg, I^2 0%), and 13 evaluated the body mass index, again showing no benefit (−0.02 kg/m^2, 95%CI −0.40 to 0.36 kg/m^2, I^2 56%). Limitations were that participants from only two smaller studies (in total 99 persons) had a mean initial TSH of > 10 mU/l and that 16 out of 19 studies had an unclear or high risk of bias in at least three of the six domains of the Cochrane bias assessment.

Conclusion
This systematic review and meta-analysis does not support the use of thyroid hormone replacement therapy in adults with subclinical hypothyroidism, at least in adults with TSH <10 mU/l.

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OC1.4

The impact of obligatory iodine prophylaxis on thyroid volume in schoolchildren

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Poland was considered as a mild-to-moderate iodine deficiency area according to results of a nation-wide survey conducted in early 1990-ties. The obligatory iodine prophylaxis program based on iodization of house-hold salt (30 mg of iodide/l kg of salt) was therefore introduced in 1997.
The aim of the study was to assess the real impact of the Polish iodine prophylaxis model on thyroid volume in schoolchildren.
Material and methods
The study included 9210 Polish schoolchildren (4731 girls, 4479 boys) aged 6–12 years, examined between 1999 and 2011. The informed written parental consent for participation in the survey was obtained for each child. 3803 of children (1909 girls and 1894 boys) were born at least one year after introduction of the iodine prophylaxis (after 12/31/1997), which meant that their mothers were using iodized salt while being pregnant. In each child TV was assessed by ultrasound (7.5 MHz linear probe) and calculated according to Brunn's formula. Body surface area (BSA) was calculated according to the following formula: weight $(kg)^{0.425}$ * height $(cm)^{0.725}$ * 71.84 * 10^{-4}. Thyroid volume was then standardized to body surface area (TV in ml divided by BSA in m^2) to minimize the influence of child age. Urinary iodine concentration (UCI) in urine casual sample was measured by Sandell-Kolthoff method.
Results
The median standardized thyroid volume (TVs) was 3.96 ml/m^2 (LQ – 3.12 ml/m^2, UQ – 4.91 ml/m^2, respectively). The median UCI was 96.2 mcg/l (LQ – 64.0 mcg/l, UQ – 142.6 mcg/l, respectively). UCI was significantly higher in children born after introduction of obligatory iodine prophylaxis (mean 118.23 ± 74.68 mcg/l vs 104.59 ± 66.80 mcg/l, $P<0.001$, Mann-Whitney U test). Age, ultrasonographic thyroid autoimmunity features, gender, UIC and date of birth (before vs. after introduction of obligatory iodine prophylaxis) were significant, independent predictors of TVs in multiple stepwise regression model.
Conclusions
Iodine prophylaxis based on iodization of household salt is effective in reduction of thyroid volume in children living in an area previously considered mildly-to-moderate iodine deficient.

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OC1.5

Low free T3 levels within the reference range independently predict cardiovascular mortality in the general population

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Introduction
Several studies have suggested an association of thyrotropin (TSH) and free thyroxine (FT4) levels within the reference range with morbidity and mortality in the general population. Low free triiodothyronine (FT3) has also been associated with a poor prognosis in several conditions. However, the association between FT3 levels within the reference range and the risk of mortality in the general population remains uncertain.
Methods
We evaluated the association between FT3 levels and mortality in 6672 adults in the National Health and Nutrition Examination Survey (NHANES) 2001–2002, 2007–2008, and 2009–2010 cycles. Thyroid function was assessed at baseline. The mortality and cause of death were prospectively evaluated until December 31, 2011. Patients with a prior history of thyroid disease, patients receiving thyroid-related drugs, and those with TSH, FT4 or FT3 outside the reference range were excluded. We categorized participants according to FT3 tertiles. We used Cox proportional hazard models to estimate hazard ratios (HR) for all-cause mortality, cardiovascular mortality, cancer-related mortality and mortality from other causes. The models were fitted unadjusted and with adjustment for potential confounders: age, gender, race, BMI, smoking, education, annual salary, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, previous cardiovascular disease, history of cancer, FT4 and TSH levels.
Results
During the follow-up period (28901 person-years, median follow-up: 45 months), a total of 353 deaths occurred (81 of cardiovascular disease, 97 of cancer and 175 of other causes). Compared to participants with FT3 levels in the upper tertile (3.3–3.9 pg/ml), participants with FT3 levels in the lower tertile (2.5–3.0 pg/ml) had higher all-cause mortality (HR 3.06 (1.71–5.45), $P<0.001$), cardiovascular mortality (HR 11.55 (3.92–34.04), $P<0.001$) and mortality from other causes (HR 2.90 (1.52–5.52), $P=0.002$). In the adjusted analysis, this association was not significant for all-cause mortality (HR 1.25 (0.66–2.38), $P=0.479$), cancer mortality (HR 1.09 (0.41–2.90), $P=0.851$) and mortality from other causes (HR 0.98 (0.41–2.38), $P=0.969$). On the other hand, compared to the highest FT3 tertile, the lowest FT3 tertile was associated with higher cardiovascular mortality, even after adjusting for confounders (HR 6.23 (1.66–23.37), $P=0.008$).
Conclusion
Low levels of FT3 within the reference range independently predict cardiovascular mortality. Our results suggest that FT3 levels may contribute to the stratification of cardiovascular risk in the general population.

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Look who is controlling your gonads!

OC2.1

The *in vivo* and *in vitro* effects of kisspeptin on human ovarian function

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Background
Infertility is a common problem and the number of couples receiving assisted reproductive treatment (ART) is increasing. Using GnRH agonists (GnRHa) to trigger oocyte maturation has been shown to reduce risk of ovarian hyperstimulation syndrome (OHSS), a common complication of IVF, compared to the more traditional use of human chorionic gonadotropin (hCG). Kisspeptin has recently been shown to be a safe trigger of oocyte maturation in women at high risk of OHSS. Kisspeptin stimulates gonadotropin secretion indirectly by stimulation of hypothalamic GnRH neurons. Kisspeptin and its receptor are also expressed in the human ovary but direct actions of kisspeptin on the ovary are unknown.

Objectives
1. To compare effects of the maturation triggers hCG, GnRHa and kisspeptin on expression, in granulosa lutein (GL) cells, of genes involved in ovarian reproductive function and steroidogenesis and 2. To examine *in vitro* effects of kisspeptin treatment on ovarian steroidogenesis in GL cells. 3. To treat GL cells *in vitro* with Kisspeptin-10 and kisspeptin-54 and to measure activation of kisspeptin receptor through calcium signal generation and protein expression of phospho-ERK and phospho-AKT.
Materials & methods
GL cells were isolated from follicular fluid collected at the time of oocyte retrieval. RNA was extracted from the cells and RT-qPCR completed comparing expression of ovarian steroidogenesis and gonadotropin receptor genes. GL cells were cultured and treated with hCG or kisspeptin and gene expression was analysed. GL cells were treated with kisspeptin-54 and kisspeptin-10 at varying dosages and timepoints.
Results
GL cells from women who received kisspeptin trigger *in vivo* showed significantly higher expression, compared to other triggers, of FSH receptor, LH/CG receptor, steroid acute regulatory protein, 3-beta-hydroxysteroid dehydrogenase type 2, aromatase, inhibins A and B, oestrogen receptors α and β. Gene expression of kisspeptin receptor was unchanged. Whereas GL cells treated *in vitro* with hcG showed the expected increase in steroidogenic gene expression, kisspeptin treatment *in vitro* had no effects. There was no evidence of activation of kisspeptin receptor after administration of kisspeptin-10 and -54.
Conclusion
Kisspeptin-54, used as an oocyte maturation trigger, augments expression of genes involved in ovarian steroidogenenesis in human granulosa cells, when compared to traditional maturation triggers. However, there was no effect of kisspeptin administration *in vitro*, indicating that the *in vivo* effects are likely to be mediated by the action of kisspeptin on gonadotropin secretion rather than by direct effects on the ovary.

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OC2.2

Overexpressed kisspeptin/Kiss1R system in human granulosa cells may be involved in the pathogenesis of polycystic ovary syndrome (PCOS) by inhibiting ovulation

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The kisspeptin/Kiss1R and neurokinin B (NKB)/ tachykinin receptor 3 (TACR3) system in the hypothalamus are essential for reproduction. Recent study suggested that the two peptide systems were both expressed in the ovary, particularly in the granulosa cells. To investigate the two systems in regulating the ovarian function, we collected the granulosa cells and follicular fluids from the 80 infertile patients (42 infertile control women and 38 PCOS women) undergoing IVF in Peking University Third Hospital. The mRNA expression of *Kiss1*, *Kiss1R*, *Tac3*, *Tacr3*, *MMP9* and *COX2* in the collected granulosa cells were tested by quantitative RT-PCR and the concentration of kisspeptin and NKB in the follicular fluids were tested using ELISA kit. Circulating levels of hormones were measured with the radioimmunoassay method. We found that *Kiss1* and *Kiss1R* were significantly upregulated in the granulosa cells from patients with polycystic ovary syndrome (PCOS) compared to the normal control (both $P<0.01$), but no significant difference was detected between the obese group (BMI$>$25) and the non-obese group (BMI$\leq$25). The expression of *Tac3* and *Tacr3* did not show significant difference between the PCOS group and normal control group, but they were significantly downregulated in the obese group (both $P<0.01$). Interestingly, both the expression of *Kiss1* and *Tac3* were highly correlated with their receptor gene, respectively (both $P<0.0001$). Additionally, *Kiss1* mRNA level was correlated with the serum AMH levels ($P<0.01$). While *Kiss1R* mRNA level was correlated with the follicular number ($P<0.05$). The expression of *Kiss1*, *Kiss1R*, *Tac3*, *Tacr3* were not significantly correlated with oocyte maturation rate and circulating hormones levels, including E_2, progesterone, follicle-stimulating hormone (FSH), luteinized hormone (LH), and E_2, progesterone, LH levels in HCG day. Kisspeptin-10 significantly inhibited the expression of *MMP9* and *COX2* in a dose-dependent manner, which were attenuated by kisspeptin antagonist, P234. Kisspeptin-10 also significantly upregulated the expression of *Tacr3*. Senktide, an agonist of TACR3, inhibited the expression of *COX2*, but not *MMP9*. Our results suggest that the overexpressed kisspeptin/Kiss1R system in human granulosa cells may be involved in the pathogenesis of PCOS by inhibiting ovulatory function of the ovary. The expression of *Kiss1* in the granulosa cells may be an alternative marker for the ovarian reserve.

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OC2.3

Whole exome sequencing in non-obstructive azoospermia allows the identification of a high-risk subgroup of infertile men for undiagnosed Fanconi Anemia, a cancer-prone disease

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Background
The etiology of non-obstructive azoospermia (NOA) remains unknown in about 40% of cases and genetic factors are likely to be involved in a large proportion of them. Gene mutations involved in stem cell proliferation and DNA repair may cause isolated NOA or be responsible for syndromic diseases, such as Fanconi Anemia (FA). Although the most frequent presenting symptom in FA is bone marrow failure in childhood, in about 10% of cases the diagnosis is delayed until adulthood and in these late-onset cases the presenting syndrome is frequently a malignant tumor.
Methods
An idiopathic NOA patient (index case) with consanguineous parents was subjected to Whole-Exome Sequencing (WES) with the purpose to identify the etiology of NOA. In the second part of the study, two-steps Sanger sequencing of the *FANCA* gene in the brother of the index case and in 27 selected NOA patients was performed. DEB-induced chromosome breakage test was carried out to confirm the FA diagnosis.
Results
Through WES we identified a rare pathogenic homozygous *FANCA* variant (c.2639G$>$A) in the index case, affected by NOA due to Sertoli Cell only syndrome (SCOS). The patient's brother (also affected by NOA) has been found to be a homozygous carrier of the same mutation. The two brothers did not manifest overt anemia, though chromosomal breakage test revealed a reverse somatic mosaicism in the index case and a typical FA picture in the brother. Following this incidental finding of FA, we selected 27 NOA patients with similar testicular phenotype and borderline/mild hematological alterations. Sanger sequencing of the *FANCA* gene in this selected group of patients allowed the identification of one additional SCOS patient showing compound heterozygous variants (c.3788_3790delTCT and c.3913C$>$T). Following our investigation, the three subjects with *FANCA* mutations are now receiving specific medical attention including strict follow-up by oncohematologists.
Conclusions
Our study reports an unexpectedly high frequency of occult FA in a specific subgroup of NOA patients with mild or borderline hematological alterations (7.1%). The screening for *FANCA* mutations in such patients may allow the identification of undiagnosed FA before the appearance of other severe clinical manifestations of the disease. Our finding highlights the importance to introduce the systematic evaluation of hematological parameters into the routine andrological workup in NOA patients. Moreover, corroborates previous epidemiological observations reporting a higher risk of morbidity (including cancer) and a lower life expectancy in infertile men in respect to fertile, normozoospermic men.

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OC2.4

Novel role of central ceramide signaling in mediating obesity-induced precocious puberty

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Childhood obesity has become a major health problem, which is coupled to different adverse outcomes and diseases. The escalating prevalence of child obesity parallels that of alterations in pubertal timing, also linked to higher disease burden later on life. Yet, the mechanisms underlying for this association remain unfolded. Ceramides, ubiquitous signaling molecules involved in numerous biological processes, have emerged as mediators of metabolic disorders and transmitters for the central actions of key hormonal regulators of metabolism and puberty. We address herein the potential contribution of central ceramide signaling to the control of puberty and its alterations due to early-onset obesity. Postnatal overnutrition of female rats, which markedly elevated body weight and advanced puberty, was associated to consistent increases of different ceramide species in the hypothalamus. Pharmacological activation of central ceramide signaling in conditions of normal nutrition partially mimicked the advancement of puberty onset caused by obesity, without changes in body weight, while its persistent blockade with the inhibitor, myriocin, delayed puberty, both in lean and obese females. Myriocin prevented also the permissive effects of the puberty-activating signal, kisspeptin, on puberty onset, but failed to alter basal gonadotropin levels, hypothalamic *Kiss1* expression or kisspeptin-induced GnRH/LH release during the peripubertal period, therefore suggesting alternative pathways. We identify here a circuit, involving the paraventricular nucleus (PVN) and ovarian sympathetic innervation, as putative conduit for such novel kisspeptin-ceramide pathway, as (i) PVN received abundant kisspeptin fibers in pubertal rats; (ii) precocious puberty linked to early-onset obesity was associated with advanced maturation of the sympathetic tone at the ovary; and (iii) virogenetic interference of ceramide synthesis at the PVN, by silencing of serine palmitoyltransferase long chain base subunit 1 (SPTLC1), partially normalized ovarian sympathetic activity and the timing of puberty onset in obese rats. All in all, our data are the first to unveil a role of central ceramide signaling in the control of pubertal timing and its alterations due to early-onset obesity. Our results disclose an alternative pathway, linking PVN ceramide synthesis and sympathetic ovarian innervation, as key for such obesity-induced precocious puberty, which may help to define better strategies for the management of pubertal disorders associated to metabolic disease.

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OC2.5

Effect of thyroxine replacement on leydig cell and sertoli cell function in men with hypothyroidism

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Background
Thyroid hormones play an important role in reproductive and sexual function in both males and females. Comprehensive information on the ill-effects of hypothyroidism on leydig cell, sertoli cell and germ cell function is lacking in the existing literature.
Objective
Our objective was to investigate the effect of hypothyroidism and its treatment on testicular function.
Patients and design
This study was carried out as a descriptive study with a before-after study design. Forty treatment naïve, overtly hypothyroid, consenting male patients were included. Hormones assessed were free T_3, free T_4, thyroid stimulating hormone, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, testosterone, inhibin B (INHB), and insulin like factor 3 (INSL3). Semen analysis was done according to WHO 2010 guidelines in 37 subjects. Sexual function questionnaires like Androgen Deficiency in Aging Male (ADAM), and Arizona Sexual Experience Scale (ASEX) were also used. All patients were treated with adequate dose of thyroxine sodium. After ensuring a euthyroid state for consecutive 6 months, reassessment of all parameters was done.
Results
At baseline, 72.5% had a low serum testosterone value ($<$ 230 ng/dl), 67.56% had low total sperm motility, 72.97% had low total progressive sperm motility, 80% had low ADAM score and 72.72% had low ASEX score. A raised prolactin level was seen in 32.5% of study subjects. Hypogonadotropic hypogonadism was more common than hypergonadotropic hypogonadism (89.66% vs 10.34%). On restoration of euthyroidism, all these parameters improved. Serum INSL3 and LH increased significantly after thyroxine replacement unlike FSH and INHB.
Conclusion
Leydig cell function was more severely affected by hypothyroidism as compared to sertoli cell function. Among sperm function parameters, motility was predominantly affected. Restoration of euthyroidism led to almost complete normalization of majority of the affected parameters.

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New insights in bone disorders

OC3.1

A Phase 3 randomized, double-blind, placebo-controlled study investigating the efficacy and safety of Burosumab, an anti-FGF23 antibody, in adult X-Linked Hypophosphatemia (XLH)

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UX023-CL303 is an ongoing, Phase 3, double-blind, multicenter study examining the efficacy and safety of burosumab, a fully human monoclonal antibody against FGF23, in adults with XLH. Eligible subjects had serum phosphorus levels <0.81 mmol/l and skeletal pain (BPI – Worst Pain ≥ 4). Subjects ($N=134$) were randomized 1:1 to receive burosumab 1 mg/kg or placebo subcutaneously every 4 weeks. After 24 weeks, subjects in the placebo group crossed-over to receive burosumab and all subjects continued treatment for an additional 24 weeks. A significantly greater percentage of subjects in the burosumab group attained the primary endpoint of mean serum phosphorus above the lower limit of normal (LLN) at the midpoint of the dosing intervals through week 24 compared with the placebo group (94.1% vs 7.6%; $P<0.0001$); increases were maintained between weeks 24–48 (crossover 89.4%, burosumab-only 83.8%). At baseline, 91 and 65 active fractures/pseudofractures (Fx/PFx) were present in 58% and 47% subjects in the crossover and burosumab-only group, respectively. At Week 24, 8% and 43% of Fx/PFx were healed after subjects received placebo and burosumab, respectively (odds ratio 16.8, $P<0.0001$). At Week 48, the burosumab-only group demonstrated additional Fx/PFx healing (63% Fx/PFx healed); the crossover group showed healing similar to that of the burosumab-only group at Week 24 (35%). For key secondary endpoints, burosumab had significantly greater decreases in stiffness score (-7.87 ± 3.04 vs 0.25 ± 3.13; $P=0.012$) than placebo at Week 24; and non-significant reductions in pain (LS mean change $\pm$ SE: burosumab -0.79 ± 0.21 vs placebo -0.32 ± 0.22; $P=0.092$) and physical functioning (-3.11 ± 2.55 vs 1.79 ± 2.72; $P=0.048$) scores. At Week 48, there were significant reductions from baseline (Week 24 for crossover) in stiffness (LS mean change $\pm$ SE: crossover -15.3 ± 3.5, burosumab-only -16.0 ± 3.3; both $P<0.0001$), physical functioning (crossover -6.4 ± 2.9, burosumab-only -7.8 ± 2.1; both $P<0.001$), and pain (crossover -1.5 ± 0.2, burosumab-only -1.1 ± 0.2; both $P<0.0001$) scores. Opioid use declined with burosumab (% subjects at Baseline, Week 24, Week 48: crossover 20%, 21%, 6%; burosumab-only 25%, 24%, 6%); NSAID use declined (crossover 65%, 58%, 17%; burosumab-only 69%, 63%, 19%). Fifteen subjects had serious AEs, none were drug-related. No meaningful changes in calcium, iPTH, or nephrocalcinosis scores occurred. Overall, burosumab was well tolerated in adults with XLH and associated with improvements in serum phosphorus, pain, stiffness, physical functioning, and Fx/PFx healing.

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OC3.2

Can a bone protein protect against muscular dystrophy?

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Receptor-activator of nuclear factor kB (RANK), its ligand RANKL and the soluble decoy receptor osteoprotegerin (OPG) are the key regulators of osteoclast differentiation and bone remodelling. Although there is a strong association between osteoporosis and skeletal muscle atrophy, the functional relevance of a particular biological pathway that regulates synchronously bone and skeletal muscle physiopathology remain elusive. We thus hypothesized that RANK/RANKL/OPG, which is a key pathway for bone regulation, is involved in Duchenne muscular dystrophy (DMD) physiopathology. Our results show that muscle-specific RANK deletion (*mdx-RANK^{mko}*) in dystrophin deficient mdx mice improves specific force (54% gain of force) of EDL muscles with no protective effect against eccentric contraction-induced muscle dysfunction. In contrast, full-length OPG-Fc injections restore dystrophic EDL muscle force (162% gain in force), protect against eccentric contraction-induced muscle dysfunction *ex vivo* and significantly improve functional performance on downhill treadmill test and post-exercise mobility. Since OPG serves as a decoy receptor for RANKL and TRAIL, *mdx* mice were injected with anti-RANKL and anti-TRAIL antibodies to decipher the dual function of OPG. Injections of anti-RANKL and/or anti-TRAIL increase significantly dystrophic EDL muscle force (45 and 17% gains of force, respectively). In agreement, truncated OPG-Fc that contains only the RANKL domains produces similar gains, in terms of force production, than anti-RANKL treatments. To corroborate that full-length OPG-Fc also acts independently of RANK/RANKL pathway, dystrophin/RANK double-deficient mice were treated with full-length OPG-Fc for 10 days. Dystrophic EDL muscles exhibited a significant gain of force relative to untreated dystrophin/RANK double-deficient mice, indicating that the effect of full-length OPG-Fc is in part independent of the RANKL/RANK interaction. In addition, one key determinant of muscle contractility and performance is the Ca^{2+} pump called sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA). SERCA captures Ca^{2+} from the cytosol into the lumen of the sarcoplasmic reticulum, making Ca^{2+} available for the next contraction. SERCA activity is significantly depressed in dysfunctional and dystrophic muscles and full-length OPG-Fc treatment restored completely SERCA activity and markedly increased SERCA-2a expression. These findings demonstrate the superiority of full-length OPG-Fc treatment relative to truncated OPG-Fc, anti-RANKL, anti-TRAIL or muscle RANK deletion in improving dystrophic muscle function, integrity and protection against eccentric contractions. In conclusion, full-length OPG-Fc may be instrumental in the development of new treatments for muscular dystrophy in which a single therapeutic approach may be foreseeable to maintain both bone and skeletal muscle functions.

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OC3.3

[^{18}F]-FDG PET/CT imaging: A tool to reveal the metabolic functions of bone marrow adipose tissue

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Introduction
White adipose tissue (WAT) and brown adipose tissue (BAT) are key regulators of systemic metabolic function. Bone marrow adipose tissue (BMAT) accounts for 10% of total adipose mass in healthy humans and therefore can be considered a third major adipose subtype. However, it is unclear if BMAT contributes to systemic energy homeostasis.
Objectives
Assess [^{18}F]-Fluorodeoxyglucose (FDG) uptake into bone and the marrow cavity (MC) following: i) insulin treatment in mice, ii) acute and chronic cold (CC) exposure in mice, or iii) conditions of BAT activation in humans.
Methods
Objective 1: mice were fasted for 4h and then treated with insulin (0.75 IU/g) or saline (0.9%), then immediately with [^{18}F]-FDG, and housed at room temperature (RT) for 1h before scanning. ***Objective 2:*** prior to [^{18}F]-FDG administration mice were fasted for 4 h at RT (control) or 4 °C (acute or CC), with CC mice further housed at 4 °C for 72 h before fasting. ***Objective 3:*** human subjects were exposed to mild cold (16 °C) for 2 h before [^{18}F]-FDG PET/CT scanning in i) participants who had received no medication or ii) three doses of prednisolone or placebo prior to attendance. All scans were analysed using PMOD software and measured activities of target tissues expressed as standard uptake values (SUV).
Results
The marrow cavity (MC) is the predominant site of [^{18}F]-FDG skeletal uptake. Insulin stimulated [^{18}F]-FDG uptake in the femur and the heart, as previously reported, but did not affect [^{18}F]-FDG uptake in the bone or MC at other skeletal sites. Despite suggestions that MAT is BAT-like, we found that neither bone nor the MC was cold-responsive during acute cold exposure. However, CC exposure profoundly increased [^{18}F]-FDG uptake in many of the tissues analysed. In cold-exposed humans, [^{18}F]-FDG uptake in the MC of the humerus and clavicle was very high, occurring at 10 and 28% of the level in BAT. Despite acutely increasing BAT activity, glucocorticoids decreased [^{18}F]-FDG uptake into the bone and had no effect of [^{18}F]-FDG uptake into the MC.
Conclusion
Glucose uptake within the MC does not respond to insulin or to acute activators of BAT. However, the MC is significant site of basal glucose uptake in humans and mice, and contributes to increased glucose uptake following CC exposure. Thus, BMAT might play a role in systemic glucose clearance and thereby influence metabolic homeostasis.

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OC3.4

Renal function change in chronic hypoparathyroidism patients treated with recombinant human parathyroid hormone (1-84) (rhPTH[1-84]) and in a historical control cohort treated with standard therapy

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Standard therapy (ST) for chronic hypoparathyroidism (HPT) includes calcium and active vitamin D supplementation, which can be associated with an increased risk of renal complications. This study compared renal function change, assessed by estimated glomerular filtration rate (eGFR) over 5 years between HPT patients receiving rhPTH1-84 as an adjunct to ST and a historical control cohort without rhPTH1-84. rhPTH1-84-treated HPT patients were selected from two single-arm, long-term, open-label studies, RACE (NCT01297309) and NCT02910466. Historical control patients were selected from the MedMining database using similar inclusion criteria to the two studies. Patients were required to have ≥ 2 eGFR measures, 5 years apart, after HPT diagnosis. Index date was defined as the baseline visit in the rhPTH1-84-treated cohort and as the 1st eligible eGFR measure date in the historical control cohort. eGFR change over time was compared using a multivariable model, adjusting for age, sex, history of hypertension, cardiac disorders, diabetes mellitus, hypercalcemia, hypocalcemia, concomitant nephrotoxic drug use, and baseline eGFR. A sensitivity analysis was conducted with a 3-year follow-up, which included patients with ≥ 2 eGFR measures, 3 years apart, after HPT diagnosis. One hundred and twenty two patients (N = 69 with and 53 without rhPTH1-84) were included in the 5-year analyses. At baseline, rhPTH1-84-treated patients were nominally younger (51.7 vs 55.8 years) and had lower eGFR (75.5 vs 82.5 ml/min per 1.73 mm^2). Race and sex were similar between cohorts. A lower proportion of rhPTH1-84-treated patients had concomitant nephrotoxic drug use or a history of hypocalcemia, hypercalcemia, hypertension, diabetes mellitus, or cardiac disorders. Characteristics were similar in the 3-year sensitivity cohorts (N = 75 with and 76 without rhPTH1-84). In the adjusted model, predicted eGFR change at year 5 was +5.80 vs −5.56 ml/min per 1.73 mm^2 in the rhPTH-treated vs historical control cohort. Annual rate of eGFR decline over 5 years of follow-up was significantly lower in rhPTH1-84-treated patients (difference in annual eGFR change = 2.13 ml/min per 1.73 mm^2; $P = 0.002$). The trend in eGFR change over 3 years was similar in the sensitivity analysis (difference in annual eGFR change = 2.96 ml/min per 1.73 mm^2; $P < 0.001$). In this non-randomized post-hoc analysis, patients with chronic HPT without rhPTH1-84 treatment exhibited significantly greater decline in eGFR than patients receiving rhPTH1-84 over 5 years, with and without adjusting for confounders. This difference was also observed over 3 years in similar cohorts. This analysis is hypothesis generating and further research is warranted.

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OC3.5

Change in bone mineral density during the first 10 years of gender affirming hormonal treatment in transwomen and transmen

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Background
Concerns about the effects of gender affirming hormonal treatment (HT) on bone mineral density (BMD) exists, particularly for transmen with decreasing estrogen levels. HT in transpersons affects BMD on short term, but long-term follow-up studies are lacking. Therefore this study aimed to investigate the change in BMD during the first 10 years of HT in adult transwomen and transmen, in order to determine whether it is necessary to assess BMD during HT.
Methods
A retrospective cohort study was performed in adult transpersons receiving HT at the VU University medical center Amsterdam (the Netherlands) between 1998 and 2015. Persons were included for analyses if they were gender affirming hormone naïve and had a dual-energy X-ray absorptiometry (DXA) scan at the start of HT. Follow-up DXA scans performed after 2, 5, or 10 years of treatment were used for analyses. The course of *Z*-scores of the lumbar spine during the first ten years of HT were analyzed using multilevel analysis, and the influence of age and serum sex hormone levels during HT were analyzed.
Results
Seven hundred and eleven transwomen (age 35 years, IQR 26–46) and 543 transmen (age 25 years, IQR 21–34) were included for analyses. Prior to the start of HT, 21.9% of transwomen and 4.2% of transmen had a low bone density, defined as a *Z*-score below −2.0. In transwomen, mean baseline *Z*-score was −0.93 (s.d. ± 1.32), which increased with +0.22 (95%CI 0.12 – 0.32) after ten years of HT. Transmen had a mean baseline *Z*-score of 0.01 (s.d. ± 1.14), which increased with +0.34 (95%CI 0.23 – 0.45) after ten years of HT. In both transwomen and transmen, *Z*-score increased more in the oldest age group (>40 years) compared with the younger age groups. In transwomen, higher estradiol level gave a higher increase in *Z*-score, while in transmen lower LH levels gave a higher increase in *Z*-score. Testosterone levels were not correlated with change in *Z*-score.
Conclusion
This study showed that HT does not have negative effects on BMD in transgender persons, which makes regularly assessment of BMD during HT not necessary. Higher estradiol levels in transwomen and lower LH levels in transmen gave a larger increase in *Z*-score, which indicates that adequate hormone substitution and therapy compliance should be stimulated. However, as even prior to HT a high percentage of low BMD is found, bone health remains an important health topic in transpersons.

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Novel insights into prediabetes and type 2 diabetes

OC4.1

Dietary intervention modulates the expression of the splicing machinery in patients at high-risk of type 2 diabetes development: clinical implications

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Development of type-2 diabetes (T2D) is critically affected by the loss of phenotypic flexibility. There is emerging evidence suggesting that, under adverse metabolic conditions, alternative mRNA splicing is markedly dysregulated at different levels. For this reason, we hypothesized that such dysregulation could contribute to loss of phenotypic flexibility. Consequently, we aimed to explore whether changes in the splicing machinery in peripheral blood mononuclear cells (PBMCs) may serve as early indicator of T2D development, and if dietary intervention could modulate the expression of these components in order to reduce the risk of T2D. Thus, the expression pattern of selected components of the major ($n=13$) and minor ($n=4$) spliceosomes, and splicing factors (SFs; $n=28$) was determined in PBMCs, isolated from basal and 4 h postprandial blood, from non-T2D patients with high-risk to develop T2D (individuals with cardiovascular event included in the CORDIOPREV study). Specifically, 107 patients developed T2D in a median follow-up of 5 years (incident-T2D) and 108 non-T2D patients were randomly selected as controls. This analysis indicated that PBMCs of incident-T2DM patients exhibited lower levels of certain spliceosome components and SFs compared to non-T2D controls, which were significantly associated to the risk of T2D development. Altogether, these results showed that incident-T2D patients had an altered expression pattern at the inclusion in the study, suggesting a potential predictive value for T2D development. As these patients were randomly assigned to one of two healthy diets (Mediterranean and low-fat diets) in order to prevent T2D development, we also analyzed the expression of the splicing machinery components in the PBMCs from basal and 4 h postprandial blood from incident-T2DM and non-T2D patients after 3 years of follow-up under the two diet conditions. Results revealed that the expression of a reduced number of spliceosome components and SFs may be influenced by diet in a different manner in incicent-T2D and non-T2D subjects, as several spliceosomal components (e.g. SPFQ and SKIP) showed an alteration in their expression level in incident-T2D patients under the different diet conditions. Interestingly, changes were most remarkable during the post-prandial phase (e.g. RNU4 and RNU11) and associated to clinical parameters. Taken together, these data revealed the existence of pre-T2D development-associated spliceosome alterations that could be modulated by the diet and could be associated to the loss of phenotypic flexibility, suggesting that these changes might help to predict the development of T2D in high-risk patients.

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OC4.2

Toe brachial index predicts major adverse cardiovascular events in patients with type 2 diabetes

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Background
Earlier identification of diabetes patients at high risk of developing cardiovascular complication will help develop new therapeutic targets for the prevention of secondary diseases and death.
Objectives
We aim to test the predictive value of toe brachial index (TBI) as a risk marker of major adverse cardiovascular events (MACE) in patients with type 2 diabetes.
Methods
TBI was measured in 741 patients with type 2 diabetes (T2D) who participated in the epidemiological study CARDIPP (Cardiovascular Risk Factors in Patients with Diabetes-a Prospective Study in Primary Care; ClinicalTrials.gov identifier NCT010497377). Conventional risk markers for vascular disease as well as non-invasive measurements for arterial stiffness; carotid-femoral pulse-wave velocity (PWV, with applanation-tonometry) and intima-media thickness of carotid arteries (IMT, with B-mode ultrasound) were estimated. Patients were followed for incidence of major acute cardiovascular events using the national Swedish Cause and death and Hospitalization registries.
Results
During the follow-up for a period of 7 years 74 patients died or were hospitalized for MACE. TBI tertiles 1 versus 3 levels (crude) were negatively related to MACE (hazard ration HR for each unit of TBI 3.02, CI 1.71 to 5.99; $P<0.001$). TBI predicted MACE independently of age, sex, diabetes duration and treatment, anti-hypertensive treatment, previous cardiovascular diseases, HbA_{1C}, LDL cholesterol, eGFR, mean ambulatory systolic BP (HR 3.16, CI 1.50–6.70; $P=0.003$). This finding of increased MACE occurrence related to low TBI levels was also statistically significant when carotid-femoral PWW, atherosclerosis plaque identification, and IMT were added to the previous model (HR 3.12, 1.32–7.35; $P=0.009$).
Conclusions
In patients with type 2, TBI predicted the incidence of MACE independently of other cardio-metabolic as well atherosclerosis risk factors.

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OC4.3

Effects of TRAIL delivery on an experimental model of type 2 diabetes and diabetic nephropathy

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Introduction
Experimental studies suggest that a circulating protein called TRAIL (TNF-related apoptosis-inducing ligand) has the potential to treat type 2 diabetes mellitus (T2DM). We have recently demonstrated that TRAIL delivery ameliorates T2DM in the high-fat diet-fed mouse. This study aimed at evaluating whether TRAIL had the potential to treat not only T2DM but also diabetic nephropathy.
Methods/design
Based on this background, 15 male db/H mice aged 8 weeks were randomly assigned to saline (CNT, $n=10$) or TRAIL treatment (CNT + T, $n=5$), together with 20 male db/db mice which were randomly assigned to saline (db/db, $n=10$) or TRAIL treatment (db/db + T, $n=10$). TRAIL was delivered at the dose of 20 microg/mouse twice per week. Body weight, food intake, fasting glucose and insulin, as well as albuminuria were measured at baseline and every 4 weeks. GTT (glucose tolerance test) and ITT (insulin tolerance test) were performed at the end of the study. Then, mice were sacrificed and bloods and tissues were collected for further analyses.
Results
In the db/db mouse, TRAIL treatment did not affect body weight and glucose metabolism, which might be due to the extreme phenotype exhibited by this genetic model of obesity. Nevertheless, TRAIL delivery significantly reduced glomerular hypertrophy and glomerulosclerosis, indicating a potential therapeutic effect on diabetic nephropathy. This might involve prosurvival/proapoptotic pathways and anti-inflammatory effects.
Conclusion
This study sheds light on TRAIL therapeutic potential against diabetic nephropathy.

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OC4.4

Association between prediabetes and incidence of chronic kidney disease, incident albuminuria, or worsening of kidney function: a secondary analysis of the SPRINT trial

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Introduction
Diabetes is a major risk factor for chronic kidney disease (CKD). Previous studies have shown contradictory results regarding the effect of prediabetes in the development of CKD.
Methods
We performed a secondary analysis of the SPRINT trial (Systolic Blood Pressure Intervention Trial) involving 9361 patients without diabetes and with an increased cardiovascular risk (clinical or subclinical cardiovascular disease, estimated glomerular filtration rate [eGFR] 20–60 ml/min per 1.73 m^2, 10-year Framingham score $\geq 15\%$, or age ≥ 75 years). We divided patients according to fasting glucose into two groups: normoglycemia (fasting glucose <100 mg/dl) and prediabetes (fasting glucose ≥ 100 mg/dl). In non-CKD patients, we assessed the incidence of CKD (decrease in eGFR $\geq 30\%$ to <60 ml/min per 1.73 m^2) and the incidence of albuminuria (doubling of the ratio of albumin/creatinine from <10 mg/g to >10 mg/g). In patients with CKD, we evaluated the incidence of a decrease in the eGFR $\geq 50\%$, the incidence of albuminuria and the development of end-stage renal disease (ESRD) requiring dialysis or kidney transplantation. We used Cox proportional hazard models to estimate hazard ratios (HR) adjusting for age, sex, race, systolic blood pressure, BMI, smoking, prior cardiovascular disease, statin and aspirin use, and trial treatment arm.
Results
In the SPRINT trial, 5425 (58.2%) patients had normoglycemia and 3898 (41.8%) had prediabetes. The prevalence of CKD was similar between groups (29.1% in normoglycemia vs 27.4% in prediabetes, $P=0.09$). During a median follow-up of 3.26 years, there were 164 (1.8%) patients with incident CKD and 245 (2.6%) with incident albuminuria among non-CKD patients. In patients with CKD, there were 21 (0.2%) patients with a decrease in the eGFR $\geq 50\%$, 108 (1.2%) with incident albuminuria and 16 (0.2%) requiring dialysis or kidney transplantation. The adjusted HR for incidence of CKD in patients with prediabetes compared with normoglycemic patients was 1.02 (0.73–1.42, $P=0.91$) and for incident albuminuria in non-CKD patients was 1.06 (0.80–1.39, $P=0.69$). Among patients with CKD at baseline, the adjusted HR for decrease in the eGFR $\geq 50\%$ in prediabetes compared with normoglycemia was 1.64 (0.64–4.22, $P=0.30$), for incident albuminuria was 0.89 (0.57–1.39, $P=0.61$), and for the development of ESRD requiring dialysis or kidney transplantation was 0.45 (0.12–1.66, $P=0.23$).
Conclusions
In the SPRINT trial, prediabetes was not associated with a higher incidence of CKD, incident albuminuria or worsening of kidney function. Prediabetes does not appear to be a relevant risk factor for development or progression of CKD.

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OC4.5

The impact of prediabetes in lung function: data from the ILERVAS project

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Background and aims
There are growing evidence supporting the deleterious effect of type 2 diabetes (T2D) on respiratory function and sleep breathing disorders. However, there is no information about the characteristics of lung function in the prediabetes stage.
Methods
We assessed pulmonary function in 3,455 non-diabetic subjects, aged between 45 and 70 years, without vascular disease nor chronic pulmonary obstructive disease from the cross-sectional study ILERVAS (ClinTrials.gov Identifier: NCT03228459). Prediabetes was defined by an HbA1c between 5.7 and 6.5%. The spirometric parameters were evaluated according to the global initiative for chronic obstructive lung disease.
Results
The entire population included 1,093 (31.6%) individuals with prediabetes and 2,362 control subjects. Subjects with prediabetes exhibited a significantly lower forced vital capacity (FVC: 93 [82;105] vs 96 [84;107] % of predicted, $P<0.001$), forced expiratory volume in the first second (FEV_1: 95 [82;108] vs 97 [85;109] % of predicted, $P=0.004$) in comparison with control subjects. In addition, a higher percentage of subjects with FVC $<80\%$ (20.7% vs 16.3%) and $FEV_1<80\%$ (19.7% vs 16.6%) was present among patients with prediabetes ($P<0.001$ for both comparisons). In the bivariate analysis, HbA1c was negatively correlated with both lung parameters (CVF: $r=-0.130$, $P<0.001$; FEV_1: $r=-0.097$, $P=0.001$) in the prediabetes group; however, this relation disappeared in the control group. Finally, in the multivariate stepwise regression analysis, HbA1c independently predicted FVC ($R^2=0.082$, $\beta=-0.062$) and FEV_1 ($R^2=0.073$, $\beta=-0.055$).

Conclusions
The negative impact of T2D in lung function seems to be present also in the prediabetes stage. Whether the preventive, diagnostic, and therapeutic measures of the 'prediabetes lung' should be initiated before the diagnosis of T2D needs to be evaluated in the next future.

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Diving deep into adrenal cortex diseases

OC5.1

Is adrenal computed tomography accurate for the diagnosis of unilateral primary aldosteronism? A retrospective international cohort study

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Background
Unilateral primary aldosteronism is the most common surgically correctable form of endocrine hypertension, usually diagnosed by adrenal vein sampling (AVS) or computed tomography (CT). We compared the outcomes of patients diagnosed by CT and AVS and determined if CT can reliably diagnose unilateral primary aldosteronism in young patients with an evident phenotype.
Methods
Patient data were obtained from 18 internationally distributed centres over 4 continents from January 1994 to June 2016. Data were retrospectively analysed for clinical and biochemical outcomes after unilateral adrenalectomy from CT ($n=235$ patients) or AVS ($n=526$ patients) management using the standardised PASO (primary aldosteronism surgical outcome) criteria.
Findings
A smaller proportion of patients achieved complete biochemical success (cure of primary aldosteronism) with CT compared with AVS management (80.0% vs 93.3%, $P<0.001$). Absent biochemical success was present in 12.3 and 1.9% of patients in the CT and AVS groups, respectively ($P<0.001$). A diagnosis by CT was associated with a decreased likelihood of complete biochemical success (adjusted OR 0.28, 0.16–0.50; $P<0.001$). The clinical outcomes between the CT and AVS groups were not significantly different but the absence of a post-surgical elevated aldosterone-to-renin ratio was a marker of complete clinical success (adjusted OR 14.8, 1.76–124.53; $P=0.013$) and of clinical benefit (complete + partial clinical success) (adjusted OR 45.5, 11.63–177.93; $P<0.001$) in the CT but not in the AVS group. In the CT group there were 11 patients aged <35 years with a single unilateral nodule (>10 mm diametre) and a normal contralateral gland. Absent or partial biochemical success (persisting primary aldosteronism) was present in three of these 11 patients and all three had baseline plasma aldosterone concentrations >554.8 pmol/l (20 ng/dl).
Interpretation
Patients with CT management for unilateral primary aldosteronism have an increased likelihood of an incorrect diagnosis (compared with AVS) and misdiagnosis can occur in young patients with a strong phenotype. Inappropriate aldosterone production driven by CT based surgery is associated with absent clinical outcomes. This supports the recommendation to perform AVS in all patients with primary aldosteronism independent of age and phenotype.

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OC5.2

Steroid profiling by liquid chromatography tandem mass spectrometry in a large cohort of patients with adrenal incidentalomas

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Background
Steroid profiling by mass spectrometry (MS) provided novel insights into the pathogenesis of adrenocortical tumors and hypercortisolism. The aims of the study were (I) to analyze the steroid profiling by liquid chromatography-tandem MS (LC-MS/MS) in a large cohort of patients with adrenal incidentalomas and (II) to investigate the relationship between steroid profile and clinical outcomes.
Methods
We included 307 patients with mono- and bilateral benign adrenal tumors, after excluding pheochromocytoma, primary hyperaldosteronism, late-onset congenital adrenal hyperplasia, and Cushing's syndrome. We classified patients as non-secreting (NS) or with subclinical hypercortisolism (SH) according to cortisol after 1 mg-dexamethasone suppression test (DST) (≤ 50 and >50 nmol/L, respectively). LC-MS/MS serum steroid profiling included cortisol, cortisone, 21-deoxycortisol, 11-deoxycortisol, 11-deoxycorticosterone, corticosterone, progesterone, 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterone (DHEA), and testosterone. Steroid profile was assessed in basal condition in all patients, after 1 mg-DST ($n=153$), and after stimulation with 1-24ACTH 250 μg ($n=91$). Data at follow-up (mean 39.6 months) were available for 207 patients.
Results
Basal steroid profiling revealed increased levels of cortisol ($P=0.001$) and 11-deoxycortisol ($P=0.002$), and lower DHEA ($P<0.001$) and androstenedione ($P<0.001$) in patients with SH vs NS. Comparable results were obtained in adenoma SH vs NS ($n=175$) and hyperplasia SH vs NS ($n=132$). 1-24ACTH stimulation revealed significant higher levels of all steroids, except for 21-deoxycortisol and androgens, in SH vs NS. Additionally, higher levels of 21-deoxycortisol ($P=0.006$) and lower levels of DHEA ($P=0.014$) and androstenedione ($P=0.034$) were observed in patients with adenoma associated with SH vs NS. Steroid profiling after 1 mg-DST revealed higher levels of cortisone, 11- deoxycortisol, and corticosterone ($P<0.001$ for all) in SH vs NS. Moreover, androgens were significantly lower in patients with SH. Logistic regression analysis showed that increasing corticosterone levels (Odds Ratio (OR) 1.122, 95% Confidence Interval (CI) 1.006–1.251, $P=0.038$) and reduced DHEA levels (OR 0.474, 95% CI 0.241–0.931, $P=0.030$) were associated with cardiovascular events, among all potential contributing factors. Increasing levels of 11-deoxycortisol were significantly associated with diabetes/impaired glucose tolerance (OR 3.002, 95% CI 1.143–7.889, $P=0.026$), with an independent contribution of age ($P=0.002$), BMI ($P=0.039$) and family history of diabetes (0.001). Patients with NS tumors who developed SH during follow-up (24/207, 11.6%) had basal lower DHEA, androstenedione, and ACTH levels, and showed higher cortisol after 1 mg-DST and larger adrenal tumors.
Conclusion
Patients with SH have a specific steroid profile with potential implications on cardiovascular and metabolic alterations.

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OC5.3

***PRKACA* L206R mutation in adrenal Cushing's syndrome makes PKA RIIβ susceptible for caspase-mediated cleavage**

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Protein Kinase A (PKA) consists of two catalytic and two regulatory subunits with several isoforms (Cα, β, γ and RIα, IIα, Iβ, IIβ, respectively). Type II regulatory subunits are phosphorylated by PKA in their inhibitory sites, while type I are not. Somatic activating mutations in the gene encoding the catalytic subunit α (Cα) of PKA (PRKACA) have been found in 30–40% of cortisol-producing adrenocortical adenomas (CPA). We recently described reduced levels of RIIβ in PRKACA-mutated CPA compared to *PRKACA* WT CPA. In NCI-H295R cells co-transfected with RIIβ and $C\alpha^{WT}$ or $C\alpha^{L206R}$, the L206R mutation led to a full degradation of RIIβ and this degradation could not be reversed by proteasome and lysosome inhibition but by caspase inhibition. Same co-transfections with RIα did not lead to its degradation. When the inhibitory site of RIIβ was replaced by the corresponding amino acids of RIα, $C\alpha^{L206R}$ did not lead to RIIβ degradation, while it was able to degrade RIα when its inhibitory site was replaced by the corresponding amino acids of RIIβ. Same results were observed

when point mutations were introduced into RIIβ or RIα in order to delete or introduce a serine into the inhibitory site (serine 114). In addition, a protein interacting with RIIβ only in $C\alpha^{L206R}$–transfected cells was identified by performing nanoLC-MS/MS analysis and interestingly, this protein is known to interact with caspases. Furthermore, a knockdown of RIIβ led to increased cortisol secretion in NCI-H295R cells. These results show that the phosphorylation of serine 114 in the inhibitory site of RIIβ plays a fundamental role in RIIβ stability and makes RIIβ susceptible for degradation in the presence of $C\alpha^{L206R}$, which is likely mediated by caspases. The resulting decreased levels of RIIβ could additionally contribute to increased cortisol levels in Cushing adenoma patients.

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OC5.4

Assessment of Tissue Sodium Content by ^{23}Na-MRI in Patients with Adrenal Insufficiency – a Pilot Study

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Introduction
Patients with chronic primary adrenal insufficiency (PAI) depend on lifelong gluco- (GC) and mineralocorticoid (MC) replacement therapy. Reduced subjective well-being is however often described by these patients in absence of clinical or laboratory abnormalities and is thus a strong indicator of the gap between the concept of adequate hormone substitution and patients' requirements. The aim of this study was to investigate the potential role of ^{23}Na-MRI for noninvasive monitoring of steroid replacement in PAI.
Methods
Sodium content (SC) was analyzed both in the calf muscle and skin of 16 patients and 16 sex-, age- and BMI-matched controls. Patients were classified into three groups (optimal, subtherapeutic, supraphysiological) according to the quality of GC and MC substitution assessed separately by clinical scores based on subjective wellbeing and clinical/laboratory parameters. Muscle and skin sodium content (Muscle-SC, Skin-SC) were determined using a ^{23}NA-MRI protocol on a 3T scanner implementing a 3D sequence.
Results
Plasma renin concentration and Muscle-SC were significantly higher in patients compared to controls (43.2 vs 11.7 ng/l, $P=0.014$ and 19.1 vs 16.0 mmol/l, $P=0.002$), whereas no significant differences in plasma/urinary electrolytes or Skin-SC were detected. These results were replicated in the subgroups receiving optimal GC and MC replacement, respectively. Skin-SC significantly correlated with 24h-urine sodium level in the whole cohort. When comparing Muscle-SC and Skin-SC with obtained clinical scores a trend from lower SC for low scores to higher SC for higher scores was observed (Table 1).
Conclusion
Interestingly, patients under sufficient replacement therapy exhibited significantly higher Muscle-SC compared to controls, whereas Skin-SC and laboratory parameters did not differ between groups. This discrepancy suggests that mechanisms involved in tissue sodium homeostasis might elude classical feedback regulation. Chronic mineralocorticoid depletion – suggested by elevated plasma renin concentration- might induce tissue sodium storage for the purpose of providing a sodium reservoir. The agreement between tissue SC and clinical scores indicates that ^{23}Na-MRI might be a quantitative method to assess steroid replacement. Further studies on a larger cohort are, however, needed to prove these initial findings.

Table 1 Tissue SC (mmol/l) according to obtained clinical scores

	Tissue SC (mmol/l)	Subtherapeutic	Optimal	Supraphysiological
GC replacement	Muscle-SC	17.27±5.15	19.21±2.12	20.96±0
	Skin-SC	15.12±1.25	16.08±3.03	18.4±0
MC replacement	Muscle-SC	18.09±2.44	19.01±3.17	20.91±0.5
	Skin-SC	15.06±2.14	15.22±2.3	18.94±3.95

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OC5.5

Cullin 3 is a partner of Armadillo Repeat Containing 5 (ARMC5), the product of the gene responsible for Primary Bilateral Macronodular Adrenal Hyperplasia

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Background
ARMC5 (armadillo repeat containing 5) has been identified as the gene responsible for PBMAH (Primary Bilateral Macronodular Adrenal Hyperplasia). *ARMC5* inactivating mutations are reported in 20 to 25% of PBMAH patients. *ARMC5*, is considered as a tumor suppressor gene controlling apoptosis and regulating steroidogenesis. The mechanisms of action of *ARMC5* are unknown. The structure of the ARMC5 protein contains ARM repeats and a BTB domain, patterns known to play a role in protein-protein interactions. Therefore identification of proteins that interact with ARMC5 and study of the mechanisms of this interaction will help to understand its function. By co-immunoprecipitation followed by mass spectrometry in HEK293 cells we identified a potential interaction between ARMC5 and Cullin3 (Cul3), also suggested in online databases and by 2 Hybrid Assay (Hu *et al*, Nat Com 2017). Cul3 is an E3 ligase that mediates the ubiquitination process and subsequent degradation of specific protein substrates. Therefore, the aim of this study was to confirm this interaction and to investigate its mechanisms.
Methods
We used immunoprecipitation experiments with HA-tagged Cul3 and the bioluminescence resonance energy transfer (BRET) proximity assay in HEK293 cells in order to confirm and investigate the interaction of ARMC5 with Cul3.
Results
ARMC5 co-immunoprecipitated with HA-Cul3 and a hyperbolic BRET saturation curve was observed with YFP-Cul3 and ARMC5-Luc indicating a specific close proximity between these two proteins. We have also observed that a missense mutation in the BTB domain (p.L754P) of ARMC5 causes the loss of its interaction with Cul3. Altogether, these complementary approaches demonstrate that ARMC5 and Cul3 form a complex involving the BTB domain of ARMC5.
Conclusion
These data demonstrate that Cul3 is an ARMC5 partner. A likely direct interaction involves the BTB domain of ARMC5 and can be altered by pathogenic ARMC5 missense mutations. This suggests that ARMC5 participates in the ubiquitination process and open new perspectives in the pathophysiology of PBMAH.

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Genetic and environmental determinants of obesity and insulin resistance

OC6.1

5β-reductase (AKR1D1) is a potent regulator of hepatic insulin sensitivity, carbohydrate and lipid metabolism *in vitro* and *in vivo*

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Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic disease. 5β-reductase (AKR1D1) is highly expressed in human liver where it inactivates steroid hormones and, in parallel, catalyzes a fundamental step in bile acid synthesis. Steroid hormones, including glucocorticoids, as well as bile acids (BAs) are established regulators of metabolic phenotype. We have hypothesized that AKR1D1 plays a crucial regulatory role in hepatic metabolic

homeostasis. Genetic manipulation of AKR1D1 (over-expression, siRNA knockdown) was performed in human liver HepG2 and Huh7 cells. Gene expression changes were confirmed by qPCR. Functional activity, assessed using gas chromatography-mass spectrometry to measure cortisone clearance and tetrahydrocortisone generation was paralleled by the anticipated changes in glucocorticoid receptor activation, as measured by luciferase reporter assays. In addition, total BA production was decreased, resulting in disturbed BA composition. RNA sequencing analysis following AKR1D1 knockdown defined discrete dysregulated metabolic pathways, notably those impacting upon insulin action and fatty acid storage and utilization. Insulin sensitivity was enhanced with increased insulin-stimulated phosphorylation of AKT, mTOR and GSK-3β following AKR1D1 knockdown. Endorsing our cellular observations, hepatic total AKT levels in 12-week AKR1D1 knockout male mice were higher than in wild-type controls, with evidence of increased phosphorylation upon insulin stimulation. *In vitro*, AKR1D1 knockdown increased glucose transporter mRNA expression with an associated decrease in extracellular glucose concentrations (15.3 ± 1.5 vs 12.1 ± 0.9 mmol/mg, $P < 0.05$) and increased intracellular glycogen accumulation (18.9 ± 0.3 vs 22.7 ± 0.3 ug/ml, $P < 0.05$). In addition, Fatty Acid Synthase (FASN) and Acetyl CoA Carboxylase 1 (ACC1) expression, the rate-limiting step in *de novo* lipogenesis, (DNL), were increased, resulting in enhanced phosphorylation of ACC and increased intracellular triglyceride accumulation (54.3 ± 12.7 vs 73.3 ± 11.0 nmol/mg, $P < 0.01$). Mass spectrometry analysis of lipid composition demonstrated increased palmitic and palmitoleic acid synthesis, consistent with increased DNL and fatty acid saturation. Cell media 3-hydroxybutyrate levels were reduced (18.7 ± 2.3 vs 11.4 ± 2.7 nmol/mg, $P < 0.01$), indicative of impaired fatty acid oxidation. Pharmacological manipulation of BA receptor activation, using the FXR agonist GW4064 and LXR antagonist 22(S)-Hydroxycholesterol, prevented the induction of lipogenic genes, suggesting that the observed metabolic phenotype is likely to be driven through BA rather than steroid hormone availability. In conclusion, AKR1D1 has the ability to regulate hepatocyte insulin sensitivity as well as carbohydrate and lipid metabolism, and therefore may have an as yet unexplored role in the pathophysiology of NAFLD.

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OC6.2

Deep transcranial magnetic stimulation acutely modulates neuro-endocrine pathways underlying obesity

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Deep Transcranical Magnetic Stimulation (dTMS) is a non-invasive modulation technique of cortical excitability that has shown to affect the mesolimbic and mesostriatal dopaminergic pathways. Consistent with these assets, dTMS is widely used as a therapeutic tool in neuro-psychiatric disorders associated with abnormal cortical excitability and dopaminergic activity, as addiction. Hence, considering the dysfuncional role of PFC and dopaminergic reward system in controlling appetite, dTMS was suggested to be affective in reducing food craving and in controlling body weight in obese subjects. However, the underlying physiological mechanisms of the dTMS effects are not fully know. Aim of this study was to investigate the effects of a single dTMS session on neuro-endocrine pathways in obesity. Fourty obese patients (11 M, 29 M; age: 48.0 ± 1.6; BMI: 36.3 ± 0.7) were assigned to receive one session of high frequency (18 Hz, HF), low frequency (1 Hz, LF) or Sham stimulation via an H-coil dTMS. H-coil was targeted to stimulate Prefrontal Cortex and Insula, bilaterally. Metabolic and neuro-endocrine parameters were evaluated before and after a single dTMS session. Following the 18 Hz dTMS session, a significant increase of norepinephrine was found (5.6 ± 0.9 vs 6.5 ± 1.2 ng/ml, $+18.0 \pm 6.8\%$, $P = 0.01$; $P = 0.05$ vs LF); a rise in β-endorphins levels was also shown (0.338 ± 0.049 vs 0.372 ± 0.048 ng/ml, $+13.9 \pm 4.6\%$, $P = 0.017$; $P = 0.010$ vs Sham; $P = 0.011$ vs LF). In the same group, glucose levels significantly increased (90.2 ± 4.1 vs 96.2 ± 4.2 mg/dl, $+7.0 \pm 1.8\%$, $P = 0.002$), whilst leptin levels significantly decreased (66.9 ± 10.5 vs 56.3 ± 9.0 ng/ml, $-16.3 \pm 3.0\%$, $P = 0.002$). Furthermore, pituitary hormones significantly decreased after a single 18 Hz dTMS session, specifically TSH (2.71 ± 0.25 vs 2.09 ± 0.18 μU/ml, $-20.7 \pm 4.7\%$, $P = 0.001$) and prolactin (17.1 ± 1.3 vs 10.6 ± 0.8 ng/ml, $-34.7 \pm 4.7\%$, $P < 0.0001$). In the LF, a significant reduction of salivary cortisol was also observed ($-29.4 \pm 9.3\%$, $P = 0.015$). These results suggest that dTMS can acutely affect orexygenic pathways and metabolic parameters mainly via modulation of the sympathetic activity and hypothalamic-pituitary-adrenal axis. The increase of β-endorphins could suggest a potential role of HF dTMS in inducing the dopaminergic system activation and therefore, in modulating the food reward system. Together these findings support the role of dTMS as a novel promising treatment for obesity.

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OC6.3

Visceral fat assessment in lamin A/C mutation carriers: phenotype – genotype correlation

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Background
Lamin A/C mutations show heterogeneous phenotypes expanding from cardiopathies to lipodystrophies. R482-*LMNA* gene mutation is the hot-spot for familial partial lipodystrophic syndromes (FPLD2) and is characterized by an increase of intra-abdominal (visceral) fat. In contrast, the visceral fat phenotype of non-R482-*LMNA* mutated patients has not been well studied.
Objectives
To compare the fat amount and visceral repartition of non-R482, R482-*LMNA* mutated patients, and non-mutated healthy controls.
Methods
This study included 29 carriers of Non-R482 lamin A/C gene mutation (non-R482 group), 29 R482-*LMNA* mutated patients, and 19 normal-weight healthy controls, in a single university hospital (Clin.gov2009-AO-1169-48). Body composition (DEXA/MRI), metabolic/inflammatory parameters, and circulating leptin levels were compared between the three groups.
Results
Gender and age did not differ between the two *LMNA*-mutated groups. R482 carriers had lower BMI (23.9 (22.2; 27.0) vs 27.5 (22.5; 29.4) kg/m^2; $P < 0.05$), leptin (5.2 (2.8; 8.0) vs 15.9 (5.2; 22.3) ng/ml; $P < 0.01$), HDL cholesterol (40 (30; 40) vs 48 (40; 50) mg/dl; $P < 0.05$) and fat mass (20 (17.7; 22.8) vs 29.7 (18.7; 38.1) %; $P < 0.001$), and higher intra/total abdominal fat ratio (0.59 (0.47; 0.67) vs 0.36 (0.22; 0.45); $P < 0.001$), fasting blood glucose (117 (94; 199) vs 91 (83; 97) mg/dl; $P < 0.001$), prevalence of diabetes ((82.7% vs 41.4%); $P < 0.01$) and hypertriglyceridemia (55.2% vs 27.6%; $P < 0.05$) than non-R482 carriers, respectively. In the control group, BMI (22 (21; 24) kg/m^2), leptin (4.6 (4.1; 10.7) ng/ml), fasting blood glucose (85 (83; 94) mg/dl, intra/total abdominal fat ratio (0.20 (0.11; 0.30)) were lower, and HDL-cholesterol (56 (44; 70) mg/dl) was higher than in *LMNA*-mutated patients, whatever the type of mutation. The fat mass (22 (20; 30) %) of the control group was intermediate between the two *LMNA*-mutated groups.
Conclusion
The non-R482 group had the highest BMI, percentage of fat mass (DEXA), and leptin level of the three groups. The intra/total abdominal fat mass and the frequency of metabolic syndrome were however intermediate between healthy controls (no metabolic syndrome) and FPLD2 who were twice more often diabetic (80%) than non-R482 mutated patients (40%). The visceral fat assessment is one of the most reliable diagnosis criteria of *LMNA*-mutated syndromes and correlates with the metabolic syndrome.

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OC6.4

Anthropometric measurements and metabolic syndrome in relation to glucocorticoid receptor polymorphisms in (local) corticosteroid users

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Introduction
Corticosteroids are amongst the most prescribed drugs and their use has been linked to cardiometabolic adverse events including weight gain and abdominal adiposity. We previously showed that users were also more likely to have the metabolic syndrome (MetS). Since an essential role in the pathway of glucocorticoid (GC) action is reserved for the glucocorticoid receptor (GR), it could be proposed that GC sensitivity altering polymorphisms could affect the vulnerability for these adverse effects. We therefore assessed the relationships between functional GR polymorphisms with anthropometric measurements and MetS in users of corticosteroids.
Methods
We included 10,619 adult participants in the population-based Lifelines cohort study. Subjects were evaluated for drug use, body mass index (BMI), waist circumference (WC), blood pressure, and fasting metabolic parameters. Genotyping was performed for GR polymorphisms associated with a relatively increased (Bcl*I* and N363S) or decreased (ER22/23EK and 9β) GC sensitivity. All included subjects had complete information on MetS components, and were classified as wild type (WT) (2 wild type alleles), GC hypersensitive (1 or 2 copies Bcl*I* and/or N363S), or GC resistants (1 or 2 copies ER22/23EK and/or 9β). Analyses were performed between nonusers (genotypes combined) and users (specified) and were adjusted for various covariates.
Results
Overall corticosteroids use was associated with a significantly higher BMI and WC in GC hypersensitive (BMI: mean difference +0.67 kg/m^2 (95% CI, 0.32–1.02); WC: +2.09 cm (1.16–3.02), both $P<0.001$), and WT users (BMI: +0.57 kg/m^2 (0.04–1.11), $P=0.04$; WC: +1.90 cm (0.48–3.31), $P<0.01$) but not in GC resistant users. In particular, the use of inhaled corticosteroids was associated with similar findings in GC hypersensitive (BMI: +1.68 kg/m^2 (1.15–2.20); WC: +4.72 cm (3.33–6.10), both $P<0.001$), and WT users (BMI: +1.07 kg/m^2 (0.25–1.89), $P=0.01$; WC: +3.53 cm (1.35–5.70), $P<0.01$). In regard to MetS, again only GC hypersensitive (odds ratio (OR) 1.23 (95% CI, 1.01–1.50)) and WT users (OR 1.43 (1.06–1.93)) were more likely to have MetS in comparison to nonusers. This was predominantly found in users of only inhaled corticosteroids (GC hypersensitive users, OR 1.44 (1.08–1.91); WT users, OR 1.64 (1.05–2.54)).
Conclusion
Corticosteroid users, in particular of inhaled corticosteroids, have an increased BMI, WC and more often MetS in comparison to nonusers. These relationships are significantly evident in carriers of GR genotypes associated with GC hypersensitivity or the wild type genotype, but not in users harboring GC resistant polymorphisms.

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OC6.5

Associations of different body fat deposits with serum 25-hydroxyvitamin D concentrations

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Introduction
Overall and abdominal obesity are both well-established risk factors of vitamin D deficiency. However, it is unclear which fat depot is most strongly related to serum 25-hydroxyvitamin D (25(OH)D) concentrations.
Objective
This study aims to distinguish specific contributions of total body fat, abdominal subcutaneous adipose tissue (aSAT), visceral adipose tissue (VAT) and hepatic fat on 25(OH)D concentrations.
Methods
This study is a cross-sectional analysis of the baseline measurements of the Netherlands Epidemiology of Obesity study, a population-based cohort study in men and women aged between 45 and 65 years. We used linear regression analyses to examine associations of total body fat, aSAT, VAT ($n=2441$) and hepatic fat ($n=1980$) with serum 25(OH)D concentrations. In the analyses we adjusted for age, ethnicity, education, chronic diseases, smoking, alcohol consumption and physical activity. Standardized values were used to compare the different adiposity measures.
Results
Mean (S.D.) age and serum 25(OH)D concentrations of the study population was 56 (6) years and 70.8 (24.2) nmol/l, respectively. Total body fat was inversely associated with 25(OH)D concentrations in women, but not in men. One percent higher total body fat was associated with 0.40 nmol/l (95%CI: −0.67–−0.13) lower 25(OH)D. VAT was inversely associated with serum 25(OH)D concentrations in both men and women. 1 cm^2 higher VAT was associated with 0.05 nmol/l (−0.09–−0.02) lower 25(OH)D in men, and 0.06 nmol/l (−0.10–−0.01) lower 25(OH)D in women. Hepatic fat was only associated with 25(OH)D in men. A tenfold increase in hepatic fat was associated with 6.21 nmol/l (−10.70–−1.73) lower 25(OH)D. aSAT was not associated with 25(OH)D concentrations in both men and women. Regressions with standardized values showed VAT was most strongly related to serum 25(OH)D concentrations.
Conclusions
The relationship between different adiposity measures and 25(OH)D concentrations was different for men and women. In women, total body fat and VAT were inversely related to 25(OH)D concentrations. In men, VAT and hepatic fat were related to 25(OH)D concentrations. In both men and women, VAT was most strongly associated with 25(OH)D concentrations. This implies that specific attention for vitamin D deficiency should be given to individuals with a high amount of VAT.

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Genomic and clinical aspects of endocrine tumours

OC7.1

Molecular classification of benign adrenocortical tumors: an integrated genomic study

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Benign adrenal tumors correspond to a spectrum of distinct tumors, including uni- and bilateral diseases with distinct morphological features, and various steroid hormone secretion types and levels. The aim is to study this variability at the molecular level using pan-genomic approaches.
Methods
One hundred and forty six benign adrenal tumors, including adrenocortical adenomas (ACA, N=), primary macronodular adrenal hyperplasia (PMAH, N=), and primary pigmented micronodular dysplasia (PPNAD, N=Cushing's disease (CD, N=) were included. ACAs secretion was either cortisol (N=), no secretion (N=), mild cortisol secretion (N=), or aldosterone (N=6). Transcriptome, methylome, miRnome and mutational status were generated using Affymetrix U133plus, Illumina Infinium 27k, Illumina sequencing or Life Technologies ampliseq targeted NGS respectively.
Results
Four main molecular groups were identified by transcriptome, methylome, miRnome and mutational status. The largest group gathered cortisol producing tumors, independently of tumor types (ACAs, PMAHs, PPNADs and CDs). These tumors all show cAMP/PKA pathway activation, by distinct mechanisms. Transcriptome identified a steroidogenic signature in this subgroup. The second group gathered the ACAs with no or mild cortisol secretion, and included the majority of beta-catenin mutations. The third group gathered PMAHs with *ARMC5* mutations, showing an ovarian expression signature. The last group was exclusively composed of aldosterone-producing ACAs, apart from other benign tumors. Epigenetic alterations and steroidogenesis seemed associated, including CpG island hypomethylation in tumors with no or mild cortisol secretion, miRNA specific patterns in different subgroups, and direct regulation of steroidogenic enzyme expression by methylation.
Conclusion
This first large-scale pangenomic characterization of benign adrenocortical lesions identifies the main molecular subgroups, and represents an important resource to for the study of adrenocortical tumorigenesis and steroidogenesis.

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OC7.2

Urine steroid metabolomics as a diagnostic tool for detection of adrenocortical malignancy – a prospective test validation study

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Background
Adrenal masses are discovered in 5% of abdominal imaging scans. Accuracy of currently available imaging tests to diagnose malignancy is poor. In a proof-of-concept study (JCE&M 2011;96(12):3775-84), we had demonstrated 90% sensitivity and specificity in detecting adrenocortical carcinoma (ACC) for urine steroid metabolomics, the combination of mass spectrometry-based steroid profiling and machine learning-based data analysis. This diagnostic performance is superior to costly imaging procedures currently used for differentiating benign from malignant adrenal masses, which lead to a high rate of unnecessary surgery. Implementation of our novel test in routine practice requires prospective validation.
Methods
We undertook a prospective multi-center international test validation study, powered to achieve recruitment of 2000 patients with an anticipated ACC rate of 5%, with prospective recruitment of patients with newly diagnosed adrenal mass >5 mm, biochemical exclusion of pheochromocytoma and 24-h urine collection; recruitment was carried out in 13 centers (11 countries) of the European Network for the Study of Adrenal Tumors (ENSAT). Urinary steroid excretion was quantified by high-throughput liquid chromatography-tandem mass spectrometry and results processed by an algorithm based on generalized matrix relevance learning vector quantization (GMLVQ). Reference standard (benign/malignant) was based on histology and imaging follow-up.
Results
We enrolled 2017 patients, 1767 (87.6%) with a benign adrenocortical adenoma (ACA), 98 (4.9%) with ACC, and 87 (4.3%) and 65 (3.2%) with other benign and malignant adrenal masses, respectively. Risk of ACC was highest in patients <40 years (13%; vs 4% in >40 years, $P<0.0001$) and adrenal masses >4 cm (20%; vs 0.13% in <4 cm, $P<0.0001$). Unenhanced CT imaging of the adrenal mass was available for 1328/1767 patients with ACA; 68% of masses had a radiodensity <10 HU indicative of a benign lesion; 17% had borderline results (10–20 HU) and 15% were suspicious of ACC (>20 HU). MRI with chemical shift indicated suspicion of ACC in 22% of 273 benign ACA. Adrenalectomy was performed in 21% (370/1767) of ACA patients. Urine steroid metabolomics demonstrated an excellent diagnostic performance with AUROC of 94.6% for 15 steroids (Sens = Spec 87.1%).
Conclusions
Overall risk of ACC in adrenal tumors is 4.9% and almost exclusively relates to adrenal masses >4 cm. ACAs are frequently misclassified as malignant by routine imaging, resulting in a high rate of imaging and unnecessary adrenalectomies. Urine steroid metabolomics demonstrates high accuracy for detection of ACC and should become standard-of-care in patients with indeterminate adrenal tumors.

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OC7.3

LncRNAs profiling reveals epigenetic heterogeneity among human parathyroid tumor

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Long noncoding RNAs (LncRNAs) are transcripts of more than 200 nucleotides not translated into proteins. They carry out diverse functions, including transcriptional regulation in *cis* or *trans*, organization of nuclear domains, and regulation of proteins or RNA molecules. Aberrant expression of LncRNAs has been reported in human cancers; indeed, data in parathyroid tumors are lacking. Based on the profiling through lncProfilers™ qPCR Array with SYBR® green detection of 90 LncRNAs in a preliminary set of 4 parathyroid carcinomas (PCas), 12 parathyroid adenomas (PAds) compared wit 2 normal parathyroid glands (PaNs), SAM significance analysis identified 9 differentially expressed LncRNAs: 3 lncRNAs were upregulated in PCas (BC200, HOXA6-AS, WT1-AS), 4 lncRNAs were downregulated in PAds (HAR1B, HOXA3-AS, MEG3, NEAT1) and 2 downregulated in both PAds and PCas compared to PaNs (KCNQ1OT1, SNHG6). The 9 lncRNAs were validated in a second independent series of parathyroid samples including 7 PCas, 6 atypical PAds, 26 PAds and 4 PaNs. Unsupervised analysis of the LncRNAs expression levels in this set of 40 parathyroid samples, identified three clusters: cluster 1 was characterized by LncRNAs general donwnregulation, cluster 3 showed LncRNAs diffuse upregulation, while cluster 2 presented an intermediate pattern. Cluster 2 included all the 4 PaNs and a subset of PAds, while clusters 1 and 3 included PCas, atypical PAds and the remaining PAds. Patients affected with cluster 2 tumors had lower total and ionized calcium as well as PTH levels than patients with clusters 1 and 3 tumors. We characterized the genetic background of the parathyroid tumors by Array Comparative Genomic Hybridization (aCGH), direct sequencing of the *MEN1* and *CDC73* genes and MLPA for the *MEN1* region. Array CGH identified monosomy of chromosome 11 in 9 (42%) PAds and loss of 1p in 7 (27%) PAds. *MEN1* mutations were detected in 5 PAds, while *CDC73* was mutated in 4 PCas. Interestingly, chromosome 11 monosomy and *MEN1* mutations were more frequent in cluster 2 PAds; cluster 1 included most PAds with loss of 1p, while PCas had wild-type *CDC73*; *CDC73*-mutated PCas were grouped in cluster 3. Considering the *MEN1* expression levels, we observed that PAds with downregulated *MEN1* mRNA levels had low KCNQ1OT1, NEAT1 and SNHG6 expression levels, suggesting an epigenetic role for menin. Experiments aimed to investigate the effect of *MEN1* silencing on the *MEN1*-associated LncRNAs are ongoing. In conclusion, parathyroid tumors show genetic and epigenetic heterogeneity affecting clinical presentation.

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OC7.4

Germline mutations in the mitochondrial 2-oxoglutarate/malate carrier (SLC25A11) gene confer predisposition to metastatic paragangliomas

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Integrative genomics studies of paragangliomas (PGL) have shown that PGL susceptibility genes are the main drivers of tumorigenesis. Comprehensive genetic analyses have identified germline *SDHB* and, to a lesser extent, *FH* gene

mutations, as predominant causes of metastatic PGL. However, some suspicious cases remain unexplained. We performed whole-exome sequencing of a paraganglioma exhibiting an *SDHx*-like molecular profile in the absence of *SDHx* or *FH* mutations and identified a germline mutation in the *SLC25A11* gene. This gene encodes the mitochondrial 2-oxoglutarate/malate carrier. Germline *SLC25A11* mutations were identified in six other patients, five of whom had a metastatic disease. These mutations were associated with loss of heterozygosity and loss of SLC25A11 protein expression, suggesting that *SLC25A11* acts as a tumour suppressor gene. Pseudo-hypoxic and hypermethylator phenotypes comparable to that described in *SDHx*- and *FH*-related tumours were observed both in tumours with mutated *SLC25A11* and in *Slc25a11*$^{\Delta/\Delta}$ immortalized mouse chromaffin knockout cells generated by CRISPR-Cas9 technology. These data show that *SLC25A11* is a novel PPGL susceptibility gene, for which loss of function correlates with metastatic presentation. Its identification expands the role of mitochondrial dysfunction in paraganglioma tumorigenesis and reveals a new pathway linking metabolic defects and cancer.

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OC7.5

Randomized trial comparing phenoxybenzamine and doxazosine for preoperative treatment of patients with a pheochromocytoma (PRESCRIPT)

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Background
Administration of α-adrenergic receptor antagonists is recommended before resection of a pheochromocytoma (PCC) in order to prevent perioperative cardiovascular complications. For this purpose either phenoxybenzamine (PXB) or doxazosin (DOX) is commonly prescribed. We conducted the first randomized controlled trial comparing the efficacy of PXB and DOX in controlling perioperative hemodynamics in patients undergoing PCC resection (ClinicalTrials.gov:NCT01379898).
Methods
Patients ≥18 years with benign PCC were randomized to pretreatment with PXB or DOX. Preoperative BP targets were: <130/80 mmHg (supine) and systolic BP 90–110 mmHg (upright). β-blockers were added if heart rate was >80/min (supine) or >100/min (upright). Anesthetic procedures were standardized. Primary endpoint was the percentage of intraoperative time outside the BP target range (i.e. MAP<60 mmHg and systolic BP>160 mmHg). Size of the study population was calculated at 134 patients. Data are presented as mean ± s.d. or median (IQR). Two-sided *P*-values <0.05 were considered significant.
Results
One hundred and thirty four patients were included (52% female), aged 54±15 years. Pretreatment with DOX ($n=68$) or PXB ($n=66$) was administered in a dose of 40 (32–48) mg and 120 (78–140) mg, respectively. BP values and heart rate just before anesthesia were not different between groups. β-receptor antagonists were initiated in 66 and 89% of the patients on DOX or PXB, respectively ($P=0.002$). Intraoperative time outside BP target range was 12 (5–20) % in the DOX group and 11 (4–21) % in the PXB group ($P=0.75$). The number of intraoperatively administered vasodilating agents was 0, 1 or >2 among 21, 34 and 45% in the DOX group, respectively. Respective percentages in the PXB group were 45, 32 and 23% ($P=0.02$). Cumulative intravenous dose of magnesium sulphate was 3 (0–4) grams in the DOX group and 0 (0–3) grams in the PXB group ($P=0.005$). The number of intraoperatively administered inotropic/vasopressive agents was 0, 1 or ≥2 among 18, 40 and 42% in the DOX group, respectively. Respective percentages in the PXB group were 26, 36 and 38% ($P=0.38$). Cumulative intravenous dose of phenylephrine and norepinephrine was 0 (0–300) μg and 137 (0–580) μg in the DOX group and 0 (0–425) μg, 55 (0–660) μg in the PXB group, respectively ($P=0.98$ and $P=0.59$).
Conclusions
The results of this RCT demonstrate an equal efficacy of DOX- and PXB-pretreatment in intraoperative hemodynamic control during PCC resection. Patients pretreated with PXB required more b-blockers preoperatively, presumably via enhanced reflex tachycardia, but fewer vasodilating agents during surgery.

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MicroRNAs as biomarkers in endocrine diseases

OC8.1

Plasma microRNA expression in patients with Cushing's disease differs from ACTH-ectopic Cushing's syndrome

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According to previous research microRNA (miR) are expressed differently in corticotropinoma and ACTH-secreting neuroendocrine tumors. MiR are released into circulation by several mechanisms and considered to be promising biomarkers.
Objective
To evaluate whether preselected miR are differently expressed in plasma samples of patients with ACTH-dependent Cushing's syndrome (CS).
Materials and methods
The blood samples were collected in the morning from fasting patients with ACTH-dependent CS and stored at −80C. Twenty three miR, which were previously reported to be differently expressed in the ACTH-secreting tumors vs healthy tissue samples (has-miR-10-5p, has-miR-129-5p, has-miR-133a-5p; has-miR-141-3p; has-miR-143-3p; has-miR-145a-5p; has-miR-150-3p; has-miR-15a-5p; has-miR-16-5p; has-miR-145-5p; has-miR-146a-5p; has-miR-150-3p; has-miR-15a-5p; has-miR-185-3p; has-miR-191-5p; has-miR-203a-5p; has-miR-210-5p; has-miR-211-5p; has-miR-31-5p; has-miR-409-3p; has-miR-431-5p; has-miR-488-3p; has-miR-7g-5p) were quantified in plasma by qPCR (Applied Biosystems, USA).
Results
We enrolled 28 patients (4 men and 24 women) with Cushing's disease (CD) with a mean age of 37 (95% CI 33–42); body mass index (BMI) 29.81 (27–32) kg/M^2 and 13 patients with ACTH-ectopic syndrome (seven men and six women with a mean age of 43 years (33–52), BMI- 30.16 (28.82–31.50) kg/M^2; and the healthy control group (2 men and 9 women) with a mean age of 39 years (33-44), BMI 28.21 (22.29-34.13) kg/M^2. Patients with ACTH-depended CS were not different in 24hUFC or ACTH levels. Among measured miRs expressions, we found statistically significant differences in the expression of miR-16-5p (45.04 (95%CI 28.77–61.31) in CD vs 5.26 (2.65–7.87) in patients with ACTH-ectopic syndrome $P<0.001$; $q=0.001$); miR-145-5p (0.097 (0.027–0.167) in CD vs no expression in ACTH-ectopic CS $P=0.008$; $q=0.087$) and less evident in miR7g-5p (1.842 (1.283–2.400) in CD vs 0.847 (0.187–1.507) in ACTH-ectopic syndrome $P=0.02$; $q=0.14$). MiR- 16-5p was differently expressed in plasma samples from healthy subjects compared to both CD and ACTH-ectopic CS. MiR- 145-5p expression differed between ACTH-ectopic CS vs healthy subjects, but not CD vs healthy subjects; whereas miR- 7g-5p was differently expressed in CD vs healthy control, but did not differ from ACTH-ectopic CS vs healthy subjects
Conclusions
Plasma miR-expression differs in patients with CD and ACTH-ectopic CS. In particular miR-16-5p, miR—145-5p and miR—7g-5p are promising biomarkers for further research to differentiate ACTH-dependent CS.

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OC8.2

MicroRNA expression profiling and functional annotation analysis of their targets in patients with diabetic kidney disease

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Context
Diabetic kidney disease (DKD) is a common microvascular complication that affects approximately 40% of patients with diabetes mellitus (DM). This complication is the leading cause of end-stage renal disease (ESRD) in patients starting renal replacement therapy and is associated with increased cardiovascular mortality. Although a tight glycemic control is able to reduce the development and delay the progression of DKD, current therapies are still not totally effective in preventing progression to ESRD. Therefore, additional mediators and mechanisms leading to DKD need to be identified for more effective diagnosis and treatment of this complication. In this context, emerging evidence suggests a role for epigenetic factors, such as microRNAs (miRNAs), in the DKD development. MiRNAs are small non-coding RNAs that regulate gene expression. Moreover, circulating miRNAs are ideal noninvasive biomarkers because they are stable in body fluids and can be detected using established techniques for quantification, such as quantitative PCR. However, the identification of the specific miRNAs expression profile involved in DKD remains incomplete.
Objective
To investigate a miRNA expression profile in plasma of type 1 DM (T1DM) patients with DKD (cases) compared to T1DM patients without DKD (controls), and to perform bioinformatic analysis to investigate the potential roles of the miRNAs.
Design
Expression of 48 miRNAs was investigated in plasma of 58 T1DM patients (23 controls, 18 with moderate DKD, and 17 with severe DKD) using Stem-loop RT-PreAmp Real-time PCR and TaqMan Low Density Array cards (Thermo Scientific Inc). Then, five differently expressed miRNAs were chosen for validation in an independent sample of 10 T1DM controls and 19 DKD cases, using RT-qPCR. Bioinformatic analyses were performed to explore the putative target genes and biological pathways regulated by these miRNAs.
Results
Nine miRNAs were differently expressed in plasma of patients with different stages of DKD (hsa-miR-141-3p, hsa-miR-16-5p, hsa-miR-192-5p, hsa-miR-204-5p, hsa-miR-21-3p, hsa-miR-215-5p, hsa-miR-29a-3p, hsa-miR-378a-5p, and hsa-miR-503-5p) compared to T1DM controls. After validation in an independent sample, hsa-miR-21-3p and hsa-miR-378-3p were upregulated; while hsa-miR-16-5p and hsa-miR-29a-3p were downregulated in DKD cases. Additionally, these miRNAs and their targets participate in pathways of known relevance for DKD pathogenesis, such as TGF-β, PI3K/Akt, longevity, AGE-RAGE signaling pathway in diabetic complications, and relaxin signaling pathways.
Conclusions
Our study demonstrates that four miRNAs were differently expressed in DKD patients, constituting potential biomarkers of this chronic diabetic complication.

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OC8.3

Circulating levels of microRNAs associate with blood pressure and left ventricular mass in primary hypertensive patients

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Introduction
MicroRNA (miRNA) has been shown to post-transcriptionally regulate physiological systems modulating blood pressure, including the adrenal biosynthesis of aldosterone. This raises the possibility that levels of specific miRNAs circulating in plasma might reflect these functional effects and have diagnostic value in the identification of hypertension and its various underlying causes. In a previous study, we measured plasma levels of miRNAs originating from the miR-24-1 cluster on chromosome 9, which correlated with the phenotype of patients with primary hypertension and primary aldosteronism. For this study, we have expanded our studies to measure a much larger array of 179 different circulating microRNAs in a population of 50 primary hypertensive patients, and assessed their correlation with relevant phenotypic traits, including systolic and diastolic blood pressure (SBP, DBP) and left ventricular mass index (LVMI).
Methods
Patients with primary hypertension ($n=50$) were drawn from the British Genetics of Hypertension (BRIGHT) study. Circulating miRNA was isolated from 200 µl EDTA plasma and analysed using Serum/Focus microRNA PCR panels (Exiqon), which employ simultaneous quantitative real-time PCR assays to measure 179 endogenous miRNAs and 13 control miRNAs. Statistical analysis was then used to identify correlation of miRNA level with phenotypic characteristics including systolic blood pressure (SBP), DBP, LVMI, age and BMI.
Results
Levels of 16 miRNAs correlated with either SBP and/or DBP ($P<0.05$). Of these, 2 miRNAs showing positive correlation with SBP or DBP, hsa-miR-28 and hsa-miR-1, were also found to correlate positively with left ventricular mass index (LVMI) in the 16 patients for whom we had this data ($P<0.05$). Interestingly, these miRNAs are each predicted to target mRNA transcribed from the *CYP11B2* (aldosterone synthase) gene. Levels of hsa-miR-27b, which originates from the miR-24-1 cluster, positively correlated with age ($P<0.05$).
Conclusions
We have expanded our analysis of circulating miRNA levels in hypertension to encompass an array of 179 miRNAs in 50 patients. Several novel associations of circulating miRNAs with SBP, DBP, LVMI and BMI have been observed. Future work will concentrate on verifying these correlations, assessing their utility for diagnostic purposes, and identifying the mechanisms by which these miRNAs target expression of specific genes and exert phenotypic effects.

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OC8.4

Detecting blood micro-RNAs and proteins associated with Graves' disease and orbitopathy

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Graves' Disease (GD) affects about 2% of the population in the UK, with female predominance. A proportion of GD patients (5–50%) develop orbitopathy (GO), which is characterized by tissue remodeling in the orbit leading to protrusion of the eye (proptosis). Blood biomarkers associated with GD or GO could be useful diagnostic or prognostic tools for researchers and clinicians. Within the framework of INDIGO IAPP-612116 (Investigation of Novel biomarkers and Definition of the role of the microbiome In Graves' Orbitopathy) we aimed at seeking proteins and microRNA (miRNA) that could be markers of the development of GD and GO in patients from three European centers. Blood samples were collected from 33 patients (14 GD, 19 GO) and 13 healthy controls from Cardiff, Milan and Essen for miRNA and protein sequencing (Illumina's HiSeq2000 and Agilent-6550 Funnel quadrupole-time-of-flight mass spectrometer). Euclidean distances based on miRNA and protein quantification were visualized through multidimensional scaling (MDS). The differential expression of miRNA and proteins among groups was analysed with multinomial regression models. Additionally, miRNA and proteins, both separately and together, were used to predict whether individuals belonged to the GD, GO or control groups. Lasso-penalised multinomial regression was used for predictions on 150 resampled datasets. This allowed the estimation, along with the accuracy of prediction, of the relative importance of specific miRNA and proteins. In total, 3025 miRNAs and 1886 proteins were detected. The MDS plot showed good separation of the three groups (GD, GO, controls). From 10-fold cross-validation, the accuracy of predictions was 0.71 or 0.81 with miRNA or protein data alone and 0.86 with miRNA and proteins combined. Comparable accuracy was measured within-group. Matching results from differential expression analysis and predictive models, 5 miRNA and 20 proteins have been identified as potential biomarkers. These include the novel miRNA Novel:19_15038, and the proteins Zonulin, Alpha-2 macroglobulin, Beta-2 glycoprotein 1 and Fibronectin. The functional analysis of miRNA targets and proteins identified relevant metabolic pathways, including hippo signaling pathway, bacterial invasion of epithelial cells, complement and coagulation cascades, longevity regulating pathway, mRNA surveillance pathway. Overall, results reveal differential expression of blood miRNA and proteins between GD and GO patients and healthy controls. Helpful biomarkers have been identified, which may be used for early diagnosis and prognosis of Graves disease, including the likelihood of its progression to orbitopathy, and represent a step forward in the direction of technology-driven precision medicine.

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OC8.5

MicroRNA profiles in diabetic octogenarians with and without historical and prospective hip fractures

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Objective
Type 2 diabetes mellitus (T2DM) patients have a higher risk for bone fractures, especially in the elderly. However, bone mineral density (BMD) does not reflect their increased bone fragility, potentially based on disturbed bone metabolism or quality. MicroRNAs are promising new biomarkers for fracture risk detection. This study aimed to find specific miRNAs in a large cohort of elderly patients with and without T2DM at risk for osteoporotic fractures.
Methods
This nursing home cohort includes 249 T2DM patients and 301 nonT2DM patients as controls. Fractures were recorded within 2 years after the first visit. Mobility scores of the patients, fracture and medical history were documented and blood samples were taken to measure bone turnover and vitamin D. miRNA sequencing using serum samples was performed by QIAGEN microRNA-seq Service. Surrogate markers were used to correlate candidate miRNAs with bone biomarkers. Target predictions were performed with online target prediction tools (miRanda, TargetScan).
Results
Mean age of the cohort was 84.4 ± 6.3 years, mean BMI 25.4 ± 4.7. Hip fractures occurred in 34% of the T2DM patients within 2 years after the first visit, compared to 15% in the nonT2DM group ($P < 0.0001$). NonT2DM patients without fractures had significantly higher mobility scores ($P < 0.01$) as compared to nonT2DM patients with fractures or the respective T2DM groups. Vitamin D levels were different between nonT2DM with- and without fracture ($P < 0.01$) but not between the T2DM and the nonT2DM patients. Comparison of miRNA sequencing results between T2DM patients with and without fractures showed specific differences in the miRNA sequencing profiles among the two groups.
Summary and Conclusion
In this cohort of very old patients with and without T2DM of comparable age and BMI, we found a very low vitamin D status, though fracture groups showed slightly higher vitamin D. We found a number of microRNA differences between diabetic fracture and non-fracture patients, with most promising candidates. MicroRNAs might serve as important biomarkers in the prediction of bone fracture risk in osteoporotic and especially T2DM patients, where existing diagnostic tools do not allow for concise fracture risk prediction.

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Thyroid from basics to clinics

OC9.1

Increased urinary iodide precedes hypothyroidism in *Dehal1* knockout mice

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Thyroid hormones (TH) synthesis requires iodine, a scarce element whose recycling is mediated by the iodotyrosine dehalogenase (encoded by the *DEHAL1* gene) through deiodination of mono- and di-iodotyrosines. In humans, biallelic mutations in *DEHAL1* lead to a severe form of congenital hypothyroidism (CH) non detectable by neonatal screening programs, which involves the risk of mental retardation. The timing and triggering factors of this particular type of hypothyroidism remain unknown and may require iodine storage depletion. Our aim was to study the amount of iodinated metabolites and TH profile in newly generated *Dehal1* knockout mice under controlled iodine diets. Heterozygus ($Dehal1^{+/-}$), homozygous ($Dehal1^{-/-}$) and Wildtype (WT) mice were fed during 4 weeks with pellets containing very low iodine amounts. Additionally, the drinking water was iodine enriched leading to three experimental groups: sufficient, non-sufficient and deficient iodine treated mice (7.0, 1.2 and 0.2 μg/day, respectively; 4 months old mice, $n = 6$ per treatment and genotype,). At the beginning (d0) and the end (d28) of the experiment, urine iodine concentration (UIC; respect to creatinine) and serum total T_4 and T_3 were determined by the Kolthof-modified method and radioimmunoassays, respectively. The status of *Dehal1* gene in knockout mice were validated via genotyping (mouse tail DNA PCR), vector gene reporter staining (X-gal for β-galactosidase activity) and tissue specific protein expression (western blot and immunohistochemistry). At d0, UIC were significantly increased ($P < 0.05$) in both $Dehal1^{+/-}$ and $Dehal1^{-/-}$ (on average, 2.8 ± 1.0 μg/ml) compared to WT mice (1.1 ± 0.6 μg/ml), while T_4 and T_3 were similar between groups (on average, 62.4 ± 5 and 0.63 ± 0.1 ng/ml, respectively). At d28, in mice undergoing iodine sufficient and deficient treatments, UIC and TH levels were similar between groups. Remarkably, under non-sufficient iodine conditions TH levels were lower in $Dehal1^{+/-}$ and $Dehal1^{-/-}$ compared to WT mice ($P < 0.05$). Our data show that an increased loss of iodine in urine anticipates a hypothyroidism in *Dehal1* deficient mice which is triggered by a non-sufficient iodine intake. Therefore, iodinated metabolites may provide new opportunities for early detection of *Dehal1* deficiency preventing mental alterations related to late diagnosed CH.

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OC9.2

Anti-tumoral effects of metformin on metastatic bone lesions of thyroid cancer

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Background
Metformin plays anti-tumoral roles in human cancers including breast and thyroid. However, its effects on metastatic lesions are undetermined. We studied the effects of metformin on bone metastasis of thyroid cancer.
Method
Luciferase-tagged anaplastic FRO and follicular FTC 133 thyroid cancer cells were used. In vivo effects of metformin were evaluated in both ectopic tumor model and bone metastasis model generated by intratibial injection.
Result
Metformin treatment significantly reduced viabilities of FRO and FTC133 thyroid cancer cells *in vitro*. However, oral administration of metformin to ectopic tumor model showed limited therapeutic effect only. To evaluate the effects of metformin in bone metastasis model, luciferase-tagged FRO or FTC133 cells were injected into tibia in nude mice and metformin was administrated via drinking water. Bioluminescence imaging showed that tumor growth was significantly decreased from 2 to 4 wks in metformin-treated tumors than controls in both FRO and FTC133 cell injected groups. In FRO cell group, total tumor volume per bone volume (TmV/BV) was significantly reduced in metformin-treated group than control by 30% at 4 weeks. The number of osteoclasts per bone was significantly decreased and the reactive bone formation was significantly reduced in metformin-treated group than in control group. To investigate the molecular mechanisms, the effect of metformin on osteoblasts in tumor microenvironment were studied. Conditioned medium of FRO (FRO-CM) was harvested and treated into murine osteoblastic cells with or without metformin. RT-PCR analysis showed that treatment of FRO-CM increased *RANKL* and decreased *OPG* while, treatment of metformin reversed FRO-CM mediated changes of *OPG/RANKL* ratio.
Conclusion
The anti-cancer effects of metformin on thyroid cancer were more sensitive in bone metastasis rather than in ectopic tumor model, owing to the regulatory actions of metformin on metastatic niche of bone.

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OC9.3

A mouse model of BRAF V600E mutated papillary thyroid cancer imitating sporadic conditions

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Introduction
Worldwide constantly rising incidence of thyroid cancer promotes research activities. Nowadays the most speculated issue is the clinical significance of BRAF mutation. For sure BRAF mutation is a cancer-specific somatic mutation consistent with papillary thyroid cancer phenotype, otherwise, its role in tumor aggressiveness, progression, and the overall poor outcome is controversial. As far as several clinical studies claim opposing opinions, the learning aspect of mouse models comes to its point.
Objective
To evaluate the effect of BRAF V600E mutation on follicular cells of the thyroid gland in a mouse model, which imitates sporadic oncogenic pathway.
Methods
A transgenic mouse model of a spontaneous Cre activation in the absence of tamoxifen leading to focal instead of global BRAF V600E activation, under the Thyroglobulin promoter, was observed at several time points. Thyroid glands of these mice underwent different immunohistochemical stainings (IHCS), that were compared with wild-type controls.
Results
BRAF V600E mutation was gradually activated in follicular cells and some areas of the thyroid gland revealed after 6 months papillary formations with typical nuclear characteristics for carcinoma. From the very beginning, the follicles and so the whole thyroid gland was growing in size, without causing breathing impairment. Blood measurements were performed, confirming normal serum levels of T_4 and TSH. The oldest sacrificed mouse, aged 18 months, shown in each of its thyroid lobes several foci of papillary thyroid carcinoma (PTC). There were mainly areas of classical PTC, then solid PTC as well as the hobnail variant pattern. The proliferative rate (including Ki67 IHCS) was overall very low. Loss of thyroglobulin expression occurred early after mutant BRAF activation i.e. before overt tumor formation. In larger tumor formations further loss of dedifferentiation was documented by the loss of E-cadherin and weaker expression of Nkx2-1 (TTF-1) in 12 months or older mice. The tumor niche did not show any rapid involvement of inflammatory cells.
Conclusion
This mouse model imitates a sporadic oncogenic tumor initiation under the activation of BRAF V600E point mutation solely expressed in follicular cells of mice thyroid gland. The model recapitulates BRAF V600E-mediated tumor initiation, development, and progression that may be used for further investigation such as drug treatment with tyrosine kinase inhibitors or solely BRAF kinase inhibitors in different phases of papillary cancer growth.

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OC9.4

Identification of an epigenetic biomarker panel for predicting the development of distant metastases in differentiated thyroid cancer

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Background
Differentiated thyroid cancer (DTC) is usually associated with an excellent prognosis. The main cause of death is due to distant metastases, but distant metastatic DTC (dmDTC) presents an interpatient heterogeneity. Some patients with distant metastases live with stable disease for many years, while others die very early. Still no effective biomarkers are available to predict either which patients will eventually develop distant metastases or what will be the final outcome of patients with dmDTC. The key for the future development of predictors probably lies in a better understanding of the (epi)genetic wiring of dmDTC. DNA methylation, one of the most studied epigenetic mechanism, affects CpG sites and is associated with transcriptional repression. While major progress has been made in understanding DNA methylation in DTC, the epigenetic architecture of dmDTC is completely unknown.
Objective
The aim of this study was to characterize the DNA methylomes of dmDTC and to identify biomarkers that predict the development of distant metastases.
Methods
We profiled DNA methylation of a series of 98 formalin-fixed paraffin-embedded tissues including 30 low risk non-metastatic DTC, 35 dmDTC, 18 metastases and 15 adjacent normal tissues using the Illumina Infinium HumanMethylationEPIC platform. We selected candidate biomarkers using the Simple Logistics classifier implemented in RWeka, and validated them by bisulfite-PCR-sequencing, bisulfite pyrosequencing and MethylQuant.
Results
We identified a signature of 156 CpGs associated with dmDTC independently of histology and mutations in BRAF and RAS. DNA methylation differed between distant metastatic (synchronous and metachronous) and low-risk non-metastatic primary tumors, while the paired primary tumor and distant metastases were similar, suggesting that molecular alterations of the primary tumors may dictate the ability to metastasize. The signature was enriched in hypomethylations and over half were located in promoters and enhancers, pointing out their role in the regulation of gene expression. We selected 10 independent CpGs with high classification power, and quantified DNA methylation by different techniques to develop a simplified quantitative and cheap assay implementable in the routine clinical practice. Based on preliminary results MethylQuant analysis appeared as the best alternative for on its simplicity, performance and cost-effectiveness.
Conclusion
We identified a 10-epigenetic biomarker panel associated with distant metastases in thyroid cancer and established new quantitative DNA methylation assays.

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OC9.5

Sentinel lymph node biopsy using methylene blue dye in papillary and medullary thyroid carcinomas and microcarcinomas in decision for lateral neck dissection

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Introduction
Surgical management of clinically N0 (cN0) patients with thyroid carcinomas remains debatable due to various reported frequencies of lymph node (LN) metastases. Preoperative ultrasound identifies only half of LN metastases found at surgery. The aim of this report was to present our experience with sentinel lymph node biopsy (SLNB) of jugulo-carotid regions, after methylene blue dye (MBD) mapping and frozen section analysis (FSA), in detection of LN metastases in lateral neck compartments and selection of cN0 patients with papillary and medullary thyroid carcinomas and microcarcinomas for additional one-time lateral neck dissection (LND).
Materials & methods
We present results of three studies from our Surgical Oncology Clinic that analyzed usefulness of *Dzodic's original SLNB method for LN staging in thyroid carcinomas* (published in *Word J Surg, 2006*): the first with 153 cN0 papillary thyroid carcinomas (PTC), the second with 111 cN0 micro-PTCs and the third with 17 cN0 medullary thyroid microcarcinomas (micro-MTC) with serum calcitonin levels <1000 pg/ml. All patients underwent injection of 1%-MBD subcapsullary in both lobes, total thyroidectomy, prophylactic central neck dissection and SLNB of jugulo-carotid regions, since blue-stained LNs in central compartment are routinely dissected. All sentinel-LNs were sent to FSA. One-time LND was performed in patients in whom FSA of sentinel-LNs showed metastases. In other patients, with benign findings, surgery was not extended.
Results
LN metastases were histologically verified in 40.9% of cN0 PTCs and 25% of cN0 micro-PTCs. Only one patient with hereditary micro-MTC had LN metastases in central and both lateral regions. *Dzodic's SLNB method* enabled detection of LN metastases in lateral neck compartments in 21% of patients. Skip

metastases were detected in about 4% of patients with PTCs and micro-PTCs, while there were no skip metastases in micro-MTCs. Method's overall accuracy was high in all studies, but the highest in the study with micro-MTCs (100%). None of the patients had allergic reactions to MBD.
Conclusion
Dzodic's SLNB method with MBD mapping and frozen section examination of sentinel-LNs from jugulo-carotid regions is accurate in detection of LN metastases in lateral neck compartments of cN0 patients with papillary and medullary thyroid carcinomas and microcarcinomas. It optimizes surgery for patients without metastases in examined sentinel-LNs and helps in decision for one-time LND in patients with histologically proven sentinel-LN metastases. This method also facilitates central neck dissection and diminishes the possibility of accidental removal of parathyroid glands (that remain non-colored), even in less experienced surgeons' hands.

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Cardiovascular aspects of endocrine diseases

OC10.1

Glucocorticoid replacement-doses and cardiovascular events in autoimmune Addison's disease – a population based retrospective cohort study

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Objective
Mortality in autoimmune Addison's disease (AAD) is increased twofold compared to matched populations. Cardiovascular disease (CVD) is the most common cause of death, but little is known of cardiovascular morbidity. Inadequate glucocorticoid replacement has been implicated in the increased risk of CVD, but evidence is lacking. The objective of this study was to examine cardiovascular morbidity and mortality in AAD, and to investigate the effects of glucocorticoid and mineralocorticoid dosing on the CVD-burden.
Methods
A population-based retrospective cohort study conducted in Sweden. The National Patient Register (NPR) and the Prescribed Drug Register (PDR) were used to identify 1500 patients with both an ICD-diagnosis consistent with AAD, and on combination treatment with hydrocortisone/cortisone acetate and fludrocortisone. 13 758 matched controls were randomly identified in the Register of Population. Patients and controls were collected 1964–2012. Drug prescription patterns were collected 2005–2012. The main outcome was CVD defined as recorded events of ischemic heart disease or cerebrovascular disease in the NPR or the Cause of Death Register. Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were analyzed using the Cox proportional hazard model. Daily doses of glucocorticoid and mineralocorticoid replacement were estimated using the PDR. Doses were stratified into tertiles to examine dose-dependent risks of CVD.
Results
AAD was associated with a significantly increased risk of CVD (HR 1.62, 95% CI 1.25–2.16). This risk remained after adjusting for diabetes and chronic obstructive pulmonary disease (HR 1.54, 95% CI 1.16–2.04). Incidence rate ratios (IRR) were 1.9 (95% CI 0.95–3.9) for intermediate-dose and 2.1 (95% CI 1.1–4.3) for high-dose glucocorticoid replacement compared to low-dose glucocorticoid replacement. For mineralocorticoids IRR were 1.1 (95% CI 0.53–2.1) for intermediate-dose and 1.4 (95% CI 0.77–2.7) for high-dose replacement.
Conclusion
Cardiovascular morbidity and mortality is increased in AAD. The risk appears to be positively correlated with increasing glucocorticoid replacement doses, but not with mineralocorticoid replacement doses.

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OC10.2

Canagliflozin attenuates the progression of atherosclerosis via reducing hyperlipidaemia and inflammation process in ApoE KO Mice

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Introduction
Treatment with sodium glucose co-transporter2(SGLT2) inhibitors was found to reduce the incidence of cardiovascular events in diabetic patients.Herein, we investigated the effects of long-term treatment with canagliflozin on atherosclerosis development in the aorta of Apolipoprotein E knockout (Apo-E$^{(-/-)}$) mice as well as on biochemical and immunohistochemical markers related to atherosclerosis.
Methods
At 4 weeks of age, mice were switched from normal to a high-fat diet. At 8 weeks of age, Apo-E$^{(-/-)}$ mice were divided into control-group (6 mice) treated with 0.5%hydroxypropyl methylcellulose per os (po.) and Cana-group (6 mice) treated with canagliflozin (10 mg/Kgr d., po.). After 5 weeks, animals were sacrificed and heart and aorta were removed. Sections stained with hematoxylin-eosin (H&E) were used for histomorphometry whereas Masson's stained tissues were used to quantify the collagen content. Aorta root sections were stained for MCP-1, CD68, a-smooth muscle actin, MMP-2, MMP-9. q-PCR experiments were carried out to quantify the mRNA expression of MMP-2, MMP-9 their inhibitors TIMP-1 and TIMP-2, IL-6, VCAM-1, ICAM-1 and MCP-1 in the aorta.
Results
Cana-group was found to have lowered LDL-cholesterol, triglycerides and glucose levels ($P<0.01$) compared to control group. Heart rate was lowered in Cana-group compared to control-group ($P<0.05$). Histomorphometry analysis revealed that one out of six mice of Cana-group vs four out of six mice in control group developed atheromatosis, while the plaque area in aortic root was significantly lower and collagen was two times more intense in Cana-group compared to control. Immunohistochemistry showed that MCP-1, a-actin and CD68 were less expressed in aortic root of Cana-group compared to control, whereas MMP-2 expression was more intense. VCAM-1 mRNA levels were lower while TIMP-1 expression was significantly higher in Cana-group compared to control. No significant differences in MMP-9, MMP-2, TIMP-2 ICAM-1 and IL-6 mRNA levels were observed between two groups. There was a decrease in MCP-1 and increase in MMP-9 mRNA expression in Cana-group compared to control, however not statistically significant.
Conclusion
Preclinical data revealed that long-term administration of Canagliflozin attenuates the progression of atherosclerosis via reducing i) hyperlipidemia and hyperglycemia, ii) inflammatory process, by lowering the expression of inflammatory molecules such as MCP-1 and VCAM-1. Moreover, Canagliflozin was found to increase the stability of atheromatous plaque through increasing the expression of TIMP-1 (MMP-2-inhibitor).

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OC10.3

ARMC5 variants and risk of hypertension in African Americans: Minority Health-GRID study

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Context
Hypertension is one of the most preventable risk factors for cardiovascular disease and death. Up to 42.1% of non-Hispanic African-American subjects have hypertension. We recently found that germline *ARMC5* variants may play a role in primary aldosteronism, particularly in African-Americans.
Objective
We investigated a cohort of participants in the Minority Health Genomics and Translational Research Bio-Repository Database (MH-GRID) study. We hypothesized a direct association between *ARMC5* variants and increased risk of hypertension in African-Americans.
Methods
MH-GRID Whole Exome Sequencing data of 1377 African-American subjects was analyzed. Cases are individuals on two or more anti-hypertensive medications of different classes, including a diuretic and controls are individuals with optimal blood pressure (BP $\leq$ 120/80 mmHg) and normal kidney function (eGFR $>$ 90 ml/min). Target single-variant and gene-based association analyses were carried out using the *ARMC5* locus information from genome-build GRCh37: chromosome $=$16, start position $=$3146941 and end position $=$31478484. Single-variant analysis of common variants (minor allele frequency, MAF $\geq$ 0.05) within *ARMC5* was conducted in PLINK 1.9. Gene-based analysis combining, common, low frequency (MAF $\geq$ 0.01 and $<$ 0.05) and rare variants (MAF $<$ 0.01) within *ARMC5* was carried out using the optimal unified kernel association test. The analyses were adjusted for age, gender, HDL, LDL, smoking and African-European admixture.
Results
44 SNPs within *ARMC5* (3 common, 4 low frequency and 37 rare variants) were considered for analysis. An *ARMC5* variant common in MH-GRID (rs116201073, MAF$=$0.07) reached nominal significance ($P=0.044$) and odds ratio (OR) $=$0.7, suggesting a protective effect for this variant. In the gene-based analysis, a set of 16 rare variants was significantly associated with hypertension (adjusted $P=0.0402$). A total of 17 variants (the 16 rare variants and rs116201073) were also significantly associated with hypertension at a lower *p*-value (adjusted $P=0.0121$).
Conclusions
We identified one common SNP of the *ARMC5* gene that was associated with risk of hypertension in African Americans and a set of 16 rare variants associated with hypertension in African Americans. These results extend our previous report of increased germline *ARMC5* variants that may be linked to severe hypertension in African-Americans, perhaps due to low-renin hypertension. Further genetic and molecular studies are needed to confirm and complement these findings.

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OC10.4

Improvement in the control of hypertension in diabetic patients screened for hyperaldosteronism

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Introduction
Control of hypertension (HT) is essential to reduce cardiovascular events in diabetic patients (DPts). However, studies indicate that only 50% of DPts with treated hypertension present adequate blood pressure (BP) control. Yet Endocrine-Society-Guideline (ESG) screening for primary hyperaldosteronism (PHA) is rarely applied. Furthermore, in patients with essential hypertension (EH), longer-acting hypertension medication (HM) improves 24-hour BP when compared to related agents with a short half-life (SHL). We evaluated the application of the ESG for PHA in DPts, and the result of therapy using only HM with an extended-half-life (EHL) in EH-DPts.
Material and methods
A retrospective observational study. Over 2 years (2013–2014), in an Endocrine-outpatient clinic, 162 consecutive patients, 73/162 DPts, were screened for PHA in application of ESG. Aldosterone/renin ration(ARR) was determined, screening considered positive with ARR$\geq$25, aldosterone and renin by RIA in pg/ml. PHA diagnosis: aldosteronemia$\geq$130 and/or ARR$\geq$50 2 hours post-25 mg captopril. Low-renin hypertension (LRH): patients not fulfilling these criteria maintaining renin levels$\leq$5.5. throughout the test, and/or basal ARR$\geq$50. These patients were changed to mineralocorticoid-receptor blockers (MRB). In the remaining patients, EH was diagnosed. If BP control was inadequate, and EH patients were receiving any SHL HM ($<$16 hours), a switch was made to EHL: Irbesartan/telmisartan, when needed amlodipine, with clorthalidone as 3rd potential agent. At least one medication was administered in the evening. Office BP was compared in DPts immediately before and 2–6 weeks post-HM modification. Results in mean (standard deviation). Student's *T*-test.
Results
In DPts. *Age:* 70.3 (12.5), age at HT diagnosis: 55.7 (13.3). Women: 53.4%. PHA: 8/73 (11%). LRH: 6/73 (8.2%), EH: 59/73 (80.8%). Main Indications for screening: moderate HT in 46.6%, severe HT in 40%. Following MRB, aldosteronism patients (PHA$+$LRH) presented a systolic BP (SBP) decrease from 146 mmHg (18.7) to 124 (7.74) ($P=0.019$), diastolic BP(DBP) from 83.6 mmHg (11.94) to 73 (9.14) ($P=0.01$). EH: 6 lost-to-follow-up. In the 37 EH with SHL, following LAM switch, SBP dropped from 148mmHg (22.6) to 126 (12) ($P=0.001$); DBP from 84 mmHg (15.3) to 71 (8.3) ($P=0.01$). The switch was accompanied by a reduction in the number of HM: from 2.21 (0.75) to 1.71 (0.6) ($P=0.007$).
Conclusions
11% of our diabetic patients with hypertension and indication for screening presented Primary Hyperaldosteronism. Given its high morbimortality, the Endocrine-Society Hyperaldosteronism Guideline should be applied in DPts. In DPts with Essential Hypertension, long-acting medication could permit improved BP control.

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OC10.5

Increased risk of antithyroid drug-induced agranulocytosis with amiodarone

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Aim
Antithyroid drugs (ATD) methimazole and propylthiouracil (PTU) are the drugs of choice for treatment of hyperthyroidism. Agranulocytosisis, the most severe side effect of these medications, occurs in 0.2–0.5% of patients. ATDs are used also in patients with amiodarone-induced thyrotoxicosis (AIT). Our objective was to evaluate the risk for agranulocytosis, associated with ATDs, in patients with AIT, and to compare the risk with the risk of ATD-associated agranulocytosis in thyrotoxicosis due to other etiologies.
Methods
A retrospective cohort study within Clalit Health Care database was conducted of all patients with thyrotoxicosis, newly treated with ATD between 1.1.2002-31.12.2015 and followed until 3 months from the last ATD prescription dispensing, or an event of agranulocytosis. High ATD dose was defined if either methimazole or PTU was administered in an average daily dose above the median dose for that drug.
Results
The cohort included 14,781 patients with thyrotoxicosis treated with ATDs. 39 patients (0.3% of the cohort) developed agranulocytosis during 40,551 years of follow-up: incidence rate 9.62 (6.84–13.15) for 10,000 years of follow up. Mean follow-up time was 2.7 years (S.D. 3.1 years). Agranulocytosis occurred after a median of 55 days. Higher ATD dose was independently associated with higher risk for agranulocytosis HR 3.53 (1.64–7.63) regardless of amiodarone. Age was also associated with increased agranulocytosis risk in univariate Cox regression analysis with HR$=$1.02 (1.01–1.04) for each 1-year increase. Five hundred ninety three of 14,781 patients were treated with amiodarone at cohort entry. 1.3% of AIT patients developed agranulocytosis on ATD therapy, as opposed to only 0.2% of patients with thyrotoxicosis due to other etiologies. In a Cox regression multivariable model amiodarone treatment at cohort entry was associated with significantly higher risk for developing agranulocytosis during ATD treatment independently of dose and age, HR 5.15 (2.10–12.60).
Conclusion
AIT patients are at increased risk for ATD-associated agranulocytosis. Higher ATD dose is an independent risk factor for agranulocytosis. We suggest closer monitoring of ATD-treated AIT patients for agranulocytosis, and initiation with lower ATD dose in AIT patients, reserving dose escalation for irresponsive cases.

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Clinical practice in endocrine tumours: combining conventional and molecular features

OC11.1

Targeted molecular analysis in adrenocortical carcinomas: a way towards improved personalized prognostication

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Adrenocortical carcinoma (ACC) has heterogeneous prognosis and no effective targeted therapies. Pan-genomic studies identified complex molecular patterns related to outcome. Our study aimed at identification of an 'easy-to-apply' molecular signature for better personalized prognostic stratification. A total of 107 ACC patients were enrolled. Clinical/histopathological parameters of prognostic relevance were evaluated. Targeted molecular analysis was performed on DNA isolated from FFPE tumor samples, including mutations and copy number alterations, methylation of promoter regions. Primary endpoint was progression-free survival (PFS). The association of age ≥ 50 years, tumor- or hormone-related symptoms, ENSAT tumor stage, resection status and ki67 proliferation index (modified GRAS classification) could prognosticate recurrence risk in the present series ($P<0.0001$; chi-square=49.0) and in an independent cohort of 368 ACC patients ($P<0.0001$; chi-square=202.5). The most frequent genetic alterations were mutations at *TP53* (22%), *CTNNB1* (17%), *NF1* (11%), *ZNRF3* (9.3%), *APC* (8.4%), *MEN1* (7.4%), and CN gains of *CDK4* (43%) and *TERT* (12%). Some recurrent mutations were also observed in genes previously not associated with ACC (e.g. *NOTCH1, CIC, KDM6A, BRCA1* and *BRCA2*). Interestingly, the combination between clinical/histopathological data and specific molecular alterations (>1 somatic mutation, alterations in Wnt/β-catenin and/or p53 pathways and high methylation pattern) showed the best prediction of PFS ($P<0.0001$; chi-square=68.6). Searching for potentially druggable targets, CN gains at *CDK4* locus and mutations affecting *NF1* or members of the DNA repair system or mismatch repair were the most frequent. This study shows the feasibility of DNA analysis on FFPE tumor tissues in the clinical practice. We demonstrate that selected clinical/histopathological parameters might predict the clinical outcome of ACC patients. However, the combination with specific molecular alterations increases the power of the prognostic stratification and may identify new potential drug targets. Our findings might pave the way to a precision medicine approach in ACC.

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OC11.2

Molecular classifiers refine the prognostic stratification of adrenocortical carcinoma

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Background
Adrenocortical cancer (ACC) is an aggressive tumour with heterogeneous prognosis. Pan-genomic studies identified molecular subgroups of ACC, remarkably associated with outcome. For routine prospective use, targeted molecular measures are needed, combined into reasonably easy and cheap techniques. The aim was to develop and validate different combinations of targeted molecular markers reflecting the molecular subgroup, and compare their prognostic value to standard prognostic factors of ACC.
Patients and methods
We performed a meta-analysis of pan-genomic studies in a training cohort of 144 ACC, determining their transcriptome (C1A or C1B), methylome (CIMP or nonCIMP), chromosomal alterations (Noisy or Chromosomal/Quiet) and mutational (Cell-cycle and Wnt-betacatenin pathways) profiles. A subset of 72 ACC was studied by targeted measures, including BUB1B-PINK1 differential expression by RT-qPCR and CpG islands methylation of 4 genes (PAX5-GSTP1-PYCARD-PAX6) by MS-MLPA. An independent cohort of 224 ACC from 21 ENSAT centers was used for prognostic validation with RT-qPCR, MS-MLPA, SNP array and targeted NGS. Analyses of disease-free survival (DFS) –for stage I-III ACC- and overall survival (OS) –for stage IV ACC- were performed using Cox models.
Results
Pan-genomic studies identified 4 molecular groups: I) C1A, CIMP and Noisy, II) C1A, (CIMP OR Noisy), III) C1A, nonCIMP and Chromosomal/Quiet and IV) C1B, showing major survival differences (logrank $P<10^{-11}$). In the training cohort, targeted measures were combined into three distinct targeted classifiers: i) a 3D-targeted classifier, recapitulating most comprehensively the pan-genomic classification, combining gene expression, chromosome alterations and methylation profiles; ii) a PCR-based classifier, measurable by PCR-based techniques, combining gene expression and methylation profiles; iii) a DNA-based classifier, using tumor DNA only and so forth combining methylation, chromosome alteration and mutational statuses. All these targeted classifiers presented a strong association with the pan-genomic molecular classification (Fisher $P<10^{-9}$). The prognostic value of targeted molecular classifiers was confirmed in the validation cohort. In localized ACC, all three molecular classifiers were identified as independent prognostic factors of recurrence (DFS HR: 5.96, 5.24 and 2.61, $P=0.003$, 0.002 and 0.006 for the 3D-, PCR-based and DNA-baseed markers respectively) in multivariable models including ENSAT stage and tumor grade. In metastatic ACC, molecular classifiers were associated with overall survival (OS HR=3.16, 4.53 and 3.02, $P=0.18$, 0.08 and 0.006 for the 3D-, PCR-based and DNA-based markers respectively in univariate analysis).
Conclusion
Molecular classification can be recapitulated with targeted molecular measures. In localized ACC, molecular classifiers are strong prognostic independent markers of recurrence, usable in clinical routine.

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OC11.3

Clinical and histopathological differences between MEN1 carriers and MEN1 phenocopy patients

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare multitumour syndrome, characterized by the occurrence of parathyroid (PHPT), pituitary adenoma (PA) and pancreatic neuroendocrine tumors (pNETs). The gene responsible is *MEN1* gene, however 10 to 20% of patients are not carriers of *MEN1* mutation. Recently, a study has shown that these patients have less aggressive course of the disease, and more favorable life expectancy than their mutation-positive counterparts. Nevertheless, their clinical and histopathological features are still unknown.
Study design
Genetic, clinical and histopathological features were analyzed in a retrospective, single-center study of 102 consecutive patients with MEN1. Direct sequencing and MLPA of *MEN1* gene were performed in all patients, and *CDKN1b* gene in *MEN1* mutation-negative patients.
Results
We found 34% of mutation-negative cases among all patients, or 47% among index cases. None of these patients had gene alterations in *CDKN1b* gene. Women were more prevalent among all patients, but this was especially pronounced in mutation-negative patients (86% vs 59% in mutation-positive, $P<0.01$). All major MEN1 tumors appeared earlier in mutation carriers, and none of mutation-negative patients had more than two major MEN1-tumors. The most frequent phenotype was PA/PHPT in mutation-negative, and PA/PHPT/pNET in mutation-positive patients. PAs were more frequent in mutation-negative than in mutation-positive patients (83% vs 57% respectively, $P<0.01$). Acromegaly appeared almost exclusively in mutation-negative patients (41% vs 3% in mutation positive, $P<0.001$). Conversely, pNETs predominantly appeared in mutation-positive (45% vs 9% in mutation-negative, $P<0.01$), and majority of them were multiple (58%). PHPT was equally distributed, but the presence of polyglandular disease was a major feature of mutation carriers (77% vs none in mutation-negative). Bronchial NETs were more prevalent among mutation-negative patients ($P<0.05$), and adrenal tumors were equally distributed ($P>0.05$). There was no difference in age of death and OS between mutation-positive and mutation-negative patients ($P>0.05$).
Conclusion
MEN1 phenocopy differs from genetically confirmed MEN1 syndrome in several aspects: the presence of only two, solitary, coexisting major MEN1-tumors that develop later in life, marked female predominance, frequently occurring acromegaly, and rare pNETs. It appears that other, non-hereditary factors are involved in initiation and development of multiple-organ NETs in MEN1 phenocopy patients. However, the contribution of low-penetrant mutations in other genes cannot be entirely excluded.

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OC11.4

Update in the genetic landscape of Cushing's Disease: TP53 and a new deubiquitinase in spotlight

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Introduction
Cushing's disease (CD) is caused by pituitary tumors hypersecreting adrenocorticotropin (ACTH). Until now somatic mutations in the 14-3-3 binding domain of Ubiquitin Specific Peptidase 8 gene (*USP8*) were the only recurring, driver mutations and were described in about 40% of the 446 CD samples that have been analysed wordwide. We wanted to assess if other driver mutations might be the pathogenetic cause of CD in those tumors without *USP8* mutations.
Methods
We performed next generation exome sequencing in matching tumor and germline DNA from 16 corticotroph tumors causing CD and 2 tumors causing Nelson's syndrome, all of them negative for *USP8* mutations. Hotspot Sanger sequencing was performed in tumor DNA from further 86 CD and 8 Nelson's tumors. *In vitro* de-ubiquitination assays were performed in transfected HeLa cells using purified K48- and K63-linked ubiquitin chains.
Results
Exome sequencing revealed *TP53* mutations in 4 out of 16 (25%) CD tumors and two in both Nelson's tumors (100%). Three were missense mutations and three, including those in the Nelson tumors, were frameshift mutations and deletions, and were distributed over the whole sequence of *TP53*. Furthermore, we found also the point missense mutation c.G1245A(p.M415I) in a new deubiquitinase, the Ubiquitin Specific Peptidase 48 gene (*USP48*) in three further samples (19%). While all tumors had other co-occuring mutations, *TP53* and *USP48* mutations were mutually exclusive in our cohort. The *USP48* mutation was found in further 10 of the 94 samples analyzed by Sanger sequencing (11%), including one Nelson tumor. This mutation increaseed significantly the deubiquitinating activity of USP48 *in vitro* both for K48 and K63 ubiquitin chains.
Conclusion
We describe here recurring mutations in *TP53* and *USP48* genes that associate with CD. *TP53* mutations suggest an impaired TP53 function in those tumors. The recurrent mutation *USP48* was shown to increase deubiquitinating activity *in vitro*, similar to those activating *USP8* mutations that have been reported in CD.

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OC11.5

Natural history of Rathke's Cleft Cysts: a multicenter experience

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Objective
Rathke's Cleft Cyst (RCC) is a common incidental type of sellar lesion, and, depending on size, may cause local mass effects with visual impairment, hypopituitarism, and headaches. In this study, we sought to define the natural history of RCC.
Methods
We performed a retrospective study of patients diagnosed with RCC between 2000 and 2016 at Stanford University Hospital, US, and Ospedale Maggiore Policlinico di Milano, Italy. Aim of the study is to investigate tumor size and pituitary function in adult patients with RCC who underwent surgery vs conservative monitoring.
Results
Patients were divided into: Group A, 72 subjects who underwent surgical resection of symptomatic RCC; and Group B, 62 subjects who did not undergo surgery and underwent serial monitoring. Compared to Group B, Group A subjects had more RCC $>$ 10 mm (79% vs 22%, $P < 0.001$); supra and extrasellar extension in 72% vs 33%, $P< 0.001$, hypopituitarism in 41.5% vs 16%, $P< 0.001$; and diabetes insipidus (DI) in 18 and 1.6% $P=0.002$, respectively. The presence of hyperprolactinemia was similar between groups (18 vs 16%). In Group A, after a mean follow up of 53.7 months, 12.5% of patients had recurrence and underwent a second surgical procedure. Surgery resulted in recovery of pituitary function in 35% of patients. Hyperprolactinemia (26.6%) and hypogonadism (66.6%) were the most common axes that recovered after surgery. Prevalence of diabetes insipidus (20.1%) did not change significantly after surgery. In addition, 16.6% of patients experienced a new pituitary deficit after surgery. In Group B, the majority of patients had stable RCC dimension with a mean follow up of 41 months: 6.4% had cyst enlargement, without need of surgical intervention. After a mean hormonal follow up of 37.2 months, no patients in Group B developed a new pituitary deficit.
Conclusion
We evaluated the natural history of RCC in subjects who underwent surgery for symptomatic RCC vs those who had conservative monitoring. Following surgery,

the majority of patients had stable remission as well as improvement in endocrine function over the 3 years follow up. In addition, subjects who are followed conservatively remained stable with regard to tumor size and hormone function. Our data offer important context in decision making about follow up of RCC patients, confirming the safety of non-surgical treatment in asymptomatic patients.

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Novel aspects of puberty development and Cushing's disease

OC12.1

Growth hormone signaling in leptin receptor expressing cells, but not in Kiss1 expressing neurons, regulates the timing of puberty

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Growth hormone (GH) is an important factor involved in the regulation of multiple biological functions. Although the influence of GH is widespread throughout several organs and tissues, the effects of GH on brain functions, such as those related to reproductive functions, are still elusive. GH deficiency or resistance can be related to late puberty onset, lack of sexual maturation and infertility. In contrast, GH therapy can accelerate puberty onset or be used to increase pregnancy rates in woman treating fertility-related problems. Thus, GH seems to modulate reproduction. However, the molecular and cellular mechanisms by which GH could potentially modulate the reproductive system are not fully understood. To understand whether GH signaling in the brain is required for sexual maturation and maintenance of reproductive functions, we used the Cre-LoxP technology to induce GH receptor (GHR) deletion in specific neuronal populations (kiss1-Cre or leptin receptor-Cre mice). Sexual maturation was assessed daily by determining the age and weight at the vaginal opening and at the first occurrence of vaginal cornification in the vaginal lavage (first estrus). These parameters were monitored daily until 80 days of age. Body weight was monitored weekly and at each specific stage of sexual maturation. The uterine mass and local fat pad mass were also determined in adult female mice. We observed that specific GHR deletion from Kiss1 expressing cells induced no effect on sexual maturation or body weight of female mice. In contrast, LepR GHR KO female exhibited delayed onset of first estrus, despite no changes on the age of vaginal opening or body weight at the specific stages of sexual maturation. However, LepR GHR KO female were lighter compare to the littermate controls throughout the development, suggesting that LepR GHR KO females need to reach a specific body weight before having sexual maturation. Accordingly, adipose fat pads weight was significantly reduced in adult LepR GHR KO females compared to control. Taking together, our results suggest that GHR expression on *Kiss1* expressing cells is not required for puberty onset in female mice. However, growth hormone signaling on LepR expressing cells seems to regulate the puberty timing. Whether the observed effects on sexual maturation are dependent on body weight needs to be further investigated.

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OC12.2

Oligogenicity in Kallmann syndrome - an underestimated phenomenon?

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Isolated hypogonadotropic hypogonadism (IHH) is caused by impaired gonadoliberin (GnRH) gene regulation, synthesis or secretion of GnRH. Genetic factors of more than 50% of the IHH are still unknown. One the most common types of IHH is the Kallmann syndrome (KS) associated with anosmia or hyposmia. In view of technological progress and new possibilities for detecting changes in human genome a comprehensive targeted analysis using next-generation sequencing (NGS) was carried out. Screening encompassed 31 patients (27 men; 4 women) with isolated hypogonadotropic hypogonadism to search for genetic background underlying IHH. The targeted sequencing of the IHH genes was conducted on Ion Torrent Personal Genome Machine™. The panel of IHH genes (dedicated library) was constructed and designed using Ion AmpliSeq™ Designer and included coding regions for 16 genes involved in the pathogenesis of IHH (e.g. *KAL1/KS1, FGFR1/KS2, PROKR2/KS3, PROK2/KS4, CHD7/KS5, FGF8/KS6, GNRHR/HH7, NELF (NSMF)/HH9, GNRH1/HH12, WDR11/HH14, HS6ST1/HH15, LRRIQ3, GLI2, OTX2, TAC3/HH10, TACR3/HH11 genes*). In 25 patients (80.6%) different mutations in examined genes were found. In 13 (52%) cases monogenic mutations were identifed, whereas in 12 (48%) cases oligogenicity (alteration present in more than one *IHH*-associated gene in a given patient) was discovered. In the literature oligogenic inheritance is reported at the level of 10–20% of all IHH cases. Our results suggest that oligogenicity in IHH could be an underestimated phenomenon. Wide NGS analysis as a high-throughput method provide a valuable insights regarding molecular mechanisms, mutational landscape and variability of the disease.

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OC12.3

Evaluation of genetic predisposition in severe and mild phenotypes of isolated hypogonadotropic hypogonadism

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Introduction
Isolated hypogonadotropic hypogonadism (IHH) often occurs in the pre-pubertal period but it can also manifest in post-puberal age. Recent position statements and guidelines differentiate between a 'true' hypogonadotropic hypogonadism, intended as congenital or acquired organic defect (characterized by frankly pathological total Testoterone values, TTe <3.5 nmol/l), and a 'false' or functional hypogonadism, associated to older age and comorbidity and characterized by a less severe reduction of TTe levels. However, there is no clear evidence that these two nosological entities are distinct from a pathogenetic point of view. We decided to investigate genetic predisposition in IHH individuals comparing them on the basis of disease onset and degree of hypogonadism.
Patients and methods
We evaluated 115 male patients affected with IHH, both normal and hypo/anosmic. Each patient underwent a genetic investigation, using Next Generation Sequencing (NGS), to search for rare, non intronic, nonsynonymous allelic variants in the candidate genes known for IHH. We performed the same analysis in 79 controls. We compared the prevalence of mutations between patients with severe hormone deficiency (sIHH: TTe ≤ 3.5 nM), patients with mild/moderate hormone deficiency (mIHH with TTe 3.5–11.0 nM but with low calculated free Te) and in controls with Te >11.0 nM).
Results
The genetic analysis showed a statistically significant difference between the prevalence of mutations in the causal genes of IHH affecting both patients with severe hypotestosteronemia and mild hormone deficiency when compared to controls ($P<0.001$ and $P<0.035$ respectively); on the contrary there was no statistically significant difference comparing the two groups of cases. BMI was similar in the groups of IHH patients (sIHH: 27.8 Kg/m^2 vs mIHH 24.75 Kg/m^2). We found no statistically significant difference in the prevalence of oligogenic defects in the two groups of cases ($P=0.75$).
Conclusions
These data suggest a similar genetic predisposition in both severe and mild phenotypes of IHH, suggesting that IHH of genetic origin is associated with a wide spectrum of GnRH disfunctions.

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OC12.4

Late-night salivary cortisol (LNSC) levels in a Phase III study of long–acting pasireotide in patients with Cushing's disease (CD)

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Introduction

LNSC has shown high sensitivity and specificity for the initial diagnosis of CD and detection of disease recurrence; however, the use of LNSC to monitor medical treatment of CD is not well established. The results of an exploratory analysis evaluating changes in LNSC in CD patients receiving long-acting pasireotide during a Phase III study (CSOM230G2304; Lacroix *et al. Lancet Diabetes Endocrinol* 2018) are reported here.

Methods

Patients ($N=150$) with persistent, recurrent or *de novo* (non-surgical candidates) CD and mean urinary free cortisol (mUFC) 1.5–5x the upper limit of normal (ULN) were randomized to monthly pasireotide 10 mg ($n=74$) or 30 mg ($n=76$). mUFC $\leq$ ULN at month (M) 7 was the primary endpoint, with change in LNSC an exploratory objective. At each time point, mean LNSC (mLNSC) was calculated as the mean of two measurements from single samples collected at 23:00 ($\pm$1 h) on the same days as the first two of three 24-hour UFC measurements. UFC and LNSC samples were analysed at central laboratories by LC-MS/MS.

Results

Mean (s.d.) mLNSC at baseline was 10.4 (8.2) nmol/l, with mLNSC > ULN (3.2 nmol/l) in 125/137 (91.2%) evaluable patients. Mean (95%CI) changes in mLNSC from baseline to M7 and M12 were −1.6 (−3.7,0.5) and −3.3 (−5.6,−1.0) nmol/l, respectively. Mean (95%CI) change from baseline to M7 in mLNSC was greatest in patients with mUFC $\leq$ ULN at M7 (−5.1 (−8.3,−2.0) nmol/l). Changes in blood pressure (BP) and weight by mUFC and/or mLNSC response among 113 evaluable patients at M7 are shown in the Table.

Mean (95%CI) percentage change from baseline to M7 in BP and weight by mUFC/mLNSC response at M7

	Both mUFC and mLNSC $\leq$ ULN $N=20$	mUFC $\leq$ ULN only $N=36$	mLNSC $\leq$ ULN only $N=5$	Both mUFC and mLNSC > ULN $N=52$
Systolic BP	−10.8 (−15.7,−5.9)	−3.9 (−7.7,0.0)	−7.4 (−16.6,1.9)	−1.2 (−3.9,1.5)
Diastolic BP	−10.5 (−16.1,−5.0)	−4.7 (−10.2,0.9)	−4.5 (−18.7,9.7)	−0.8 (−4.6,2.9)
Weight	−5.7 (−9.1,−2.3)	−3.7 (−5.8,−1.6)	−2.0 (−10.9,7.0)	−4.3 (−5.8,−2.7)

Conclusion

Long-acting pasireotide decreased mLNSC levels, with greatest reductions seen in patients with controlled mUFC at M7. More patients achieved normal mUFC than normal mLNSC at M7, with few patients having normal mLNSC but elevated mUFC. Greatest reductions in BP were seen for patients with normal mUFC and mLNSC. Further studies designed to assess the effect of medical therapies on LNSC in CD patients are warranted.

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OC12.5

Diabetes mellitus and muscle weakness are independently associated with mortality in patients with Cushing's syndrome. Data from ERCUSYN

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Background

Patients with active Cushing's syndrome (CS) have increased mortality.

Aims

Evaluate cause of death in a large cohort of CS patients, and establish factors associated with increased mortality.

Methods

We analysed 1514 patients included in the European Registry on Cushing's syndrome (ERCUSYN): 1022 (68%) had pituitary-dependent CS (PIT-CS), 379 (25%) adrenal-dependent CS (ADR-CS), 71 (5%) had an ectopic source (ECT-CS) and 42 (3%) other causes (OTH-CS). Median duration of follow-up was 139 weeks.

Results

Fifty-one patients died (3.3%): 23 (2.2%) PIT-CS, 7 (1.8%) ADR-CS, 18 (20%) ECT-CS and three (6.7%) OTH-CS. The commonest cause of death in patients with PIT-CS and ADR-CS were infectious ($n=8$), cardiovascular ($n=3$), and cerebrovascular diseases ($n=3$). The commonest cause of death in patients with ECT-CS was progression of the underlying tumor ($n=10$), infections ($n=3$) and cardiovascular disease ($n=2$). The median (interquartile range) time from diagnosis to death was 67 (11–203) weeks in patients with PIT-CS and ADR-CS and 9 (3.6–48) weeks in patients with ECT-CS ($P=0.007$). Patients who died had a higher prevalence of diabetes mellitus (59 vs 35%; $P=0.001$) and muscle weakness (86 vs 69%; $P=0.012$) at diagnosis. The prevalence of hypertension, skin manifestations and depression at diagnosis did not differ between groups. By regression analysis, age (Odds ratio (OR) 1.05 (95% CI 1.02–1.07); $P<0.001$), diabetes (OR 2.14 (95% CI 1.07–4.27); $P=0.030$), and muscle weakness (OR 2.5 (95% CI 1.01–6.15); $P=0.045$) were significantly associated with mortality. Of 51 deceased patients, 23 (45%) died within 90 days from start of treatment and 3 (6%) before any treatment initiation. Of these, 7 (33%) had PIT-CS, 5 (24%) had ADR-CS, 12 (57%) had ECT-CS, and 2 (10%) OTH-CS. The commonest cause of death in these patients was infection ($n=9$). Two-thirds of patients who died within 90 days from start of treatment had diabetes, vs.35% in the whole ERCUSYN cohort ($P=0.001$). By regression analysis, age (OR 1.06 (95% CI 1.03–1.10); $P<0.001$) and diabetes mellitus (OR 2.9 (95% CI 1.1–7.2); $P=0.025$) were independently associated with death within 90 days from start of treatment.

Conclusion

Mortality was highest in patients with ectopic CS. Irrespective of etiology, older age, muscle weakness and diabetes at diagnosis were independently associated with increased mortality. Infectious diseases were the commonest cause of death soon after diagnosis and initiation of treatment, and patients with diabetes mellitus seem to be especially vulnerable, emphasizing the need for careful clinical vigilance at that time.

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The curious case of growth hormone

OC13.1

Postoperative use of somatostatin analogs and mortality in patients with acromegaly

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Objective
To assess the effect of somatostatin analogs (SSTA) on mortality in relation to metabolic control of acromegaly after pituitary surgery.
Design
A retrospective study in two large tertiary referral centers in The Netherlands.
Patients and methods
Three hundred and nineteen patients with acromegaly in whom pituitary surgery was performed as primary therapy between January 1980 and July 2017 were included (total follow-up: 3887 patient years). Postoperative treatment with SSTA was prescribed to 174 (55%) patients because of persistent or recurrent disease. Metabolic control at last visit was assessed by local IGF1 standard deviation score (SDS). Adequate metabolic control was defined as an IGF-1 SDS $\leq$ 2. Univariate determinants of mortality and standardized mortality ratios (SMR) were calculated for groups with and without SSTA at any moment postoperatively and at last visit.
Results
In total, 27 deaths were observed. SSTA use was not associated with increased mortality. In univariate analysis, determinants of mortality were inadequate metabolic control (RR 3.41, $P=0.005$), surgery by craniotomy/combined approach (RR 3.53, $P=0.013$) and glucocorticoid substitution (RR 2.11, $P=0.047$). The SMR of patients with adequate metabolic control who used SSTA at any moment postoperatively (1.06, $P=0.959$) and at last visit (1.19; $P=0.769$) was not increased. Insufficiently controlled patients had a significantly raised SMR (3.94, $P<0.001$).
Conclusion
Postoperative use of SSTA is not associated with increased mortality in patients with acromegaly when adequately controlled. In contrast, inadequate metabolic control, primary surgery by craniotomy/combined approach, and glucocorticoid substitution are associated with increased mortality.

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OC13.2

Time trends of mortality in patients with GH secreting and non-functioning pituitary adenoma

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Background and aims
Patients with GH secreting or nonfunctioning pituitary adenoma (NFPA) have high mortality ratios, despite enhancement of the old therapies. The aim of the study is to analyze the relationship between mortality and risk factors, including therapy, in patients with acromegaly (ACM) and NFPA evaluated in the last 16 years.
Methods
We evaluated retrospectively 749 patients with pituitary adenoma (435F/314M), 386 with ACM and 363 with NFPA, between 2001–2007 and 2008–2016. Standard mortality ratio (SMR) was calculated as the ratio between observed and expected number of deaths. A multivariable Cox regression was used to calculate hazard ratios (HR) for all-cause mortality risk factors.
Results
In patients with ACM- follow-up 3286.88 person-years (median 8.5 years), mortality ratio was increased (observed deaths: $n=62$) against expected ($n=38$): SMR = 1.60 (95% Confidence Interval (CI) 1.23–2.06), while in NFPA- follow-up 2570.70 person-years (median 7.5 years), SMR was 1.38 (95% CI 1.05–1.79). Females with both ACM and NFPA had doubled mortality ratio: SMR = 2.19 (95% CI 1.57–2.98) and 2.00 (95% CI 1.28–2.97), respectively. At multivariate regression analysis, age, post-treatment GH and tumor diameter were independently correlated to mortality in ACM (HR 1.085 (95%CI 1.058–1.114, $P<0.001$; HR 1.018 (95%CI 1.006–1.031, $P=0.003$), and respectively HR 1.041 (95%CI 1.004–1.080, $P=0.03$), while age and remnant tumor diameter were correlated to mortality in NFPA patients (HR 1.07 (95%CI 1.044–1.099, $P<0.001$ and respectively HR 1.02(95%CI 1.008–1.051, $P=0.018$)). Patients diagnosed before 2008 died more frequently than patients diagnosed since 2008 (109/415 vs 14/334, respectively), but with longer follow-up (10.99 ± 3.94 vs 4.34 ± 2.45 years, respectively). Regarding pituitary tumor treatment, proportion of patients with ACM receiving neurosurgery (58.5% before 2008 vs 73.68% since 2008, $P=0.002$), radiotherapy (61.96% before 2008 vs 20.39% after 2008, $P<0.001$) and medical treatment (52.13% vs 65.13%, $P=0.008$) changed, but the ratio of cured and medically controlled ACM did not changed (54.93%vs 56.57%, respectively, $P=0.06$). Pituitary insufficiency was more frequent in patients diagnosed before 2008 on all axes (gonadic/thyroid/adrenal: 37.17/26.49/16.66%) vs patients diagnosed after 2008 (21.19/11.92/5.9%, respectively), reflecting the greater proportion of irradiated patients and longer follow-up. Average post treatment GH, IGF1 levels and pituitary tumor remnant diameter were not different before or after 2008.
Conclusion
Patients with GH secreting or nonfunctioning pituitary adenoma had still high mortality ratios, especially in females. Efficacy of changes in therapy after 2008 need longer follow up to see changes in mortality.

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OC13.3

Molecular profiling for assistance to pharmacological treatment of acromegaly

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Pharmacologic treatment of acromegaly is currently based upon assay-error strategy in which first generation somatostatin analogs (SSA) is the first-line treatment. However, about 50% of patients do no respond adequately to SSA. We aimed to evaluate the potential usefulness of including studies of molecular markers identifying poor response to SSA for prescription of pharmacologic treatment in acromegalic patients in which SSA was prescribed before surgical therapy.
Methods
Retrospective study in which 68 acromegalic patients (59% females, median age 44) from a national cohort from 12 hospitals participated. All patients were treated with SSA preoperatively during at least 6 months under maximal effective therapeutic doses according to IGF-I values normalization. Response to SSA treatment was categorized as: complete response (C) when IGF-I achieved normal values; partial (P) response if IGF-I was between $>2<3$ SDS requiring combined treatment with pegvisomant or non-responders (NR) when IGF-I was >3 SDS and patient required monotherapy with pegvisomant. Somatotropinoma tissue from surgical specimen was obtained, RNA-later embedded and further processed for evaluation of the expression of 11 genes related to SSA response: *SSTR2*, *SSTR5*, *AIP*, e-cadherin (*CDH1*), Ki67, Kallikrein 10 (*KLK10*), arrestin beta-1 (*ARRB1*), ghrelin (*GHRL*), intron 1 Ghrelin (*in1-Ghrelin*), ZAC1

(*PLAGL1*) and Raf Kinase inhibitory protein (*PEBP1*). Measurements were made by RT-qPCR and obtained levels were normalized by the expression of *MRPL19*, *TBP* and *PGK1* as reference genes. Furthermore, we analysed the gene GNAS (*gsp*) looking for mutations in the 201 and 227 codons using conventional PCR and Sanger Sequencing.
Results
According to therapeutic response there were 26 patients (38%) with complete, 17 (25%) with partial response and 25 (37%) no response. SSTR2 expression and CDH1 were associated to complete response ($P=0.05$ and $P<0.001$, respectively). Moreover, CDH1 was able to discriminate between the three different therapeutic response categories (C, P, NR) None of the other previously described genes related to SSA therapeutic response showed statistically significant different expression between C, P or NR patients. The best discriminator between C and NR was CDH1 (ROC AUC=0.74, $P<0.01$).
Conclusions
Somatotropinomas are heterogeneous tumours depicting a high variable molecular expression of genes associated to SSA response. CDH1 is the best molecular discriminator of therapeutic response to SSA. Thus, it may be useful in subsequent treatment decision after surgical failure in acromegalic patients.

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OC13.4

Effects of pegvisomant on glucose metabolism in acromegaly: A meta-analysis of prospective interventional studies

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Introduction
Glucose metabolism impairment is a common complication of acromegaly. Pegvisomant (PEG) is used as second-line medical treatment in acromegaly. Data from literature suggest a positive effect of PEG on glucose metabolism but a meta-analysis has never been performed.
Aim
To address the following questions: i) does PEG affect glucose metabolism? ii) does the effect correlate with disease control?
Methods
We performed a meta-analysis of prospective interventional studies reporting the use of PEG for the treatment of acromegaly. We searched MEDLINE, EMBASE, and SCOPUS for English-language studies. Inclusion criteria: minimum 6-month follow-up, glyco-metabolic outcomes before and after PEG treatment. The pooled estimate of a weighted mean was obtained for all outcomes using a random effects model.
Results
Fifteen studies met inclusion criteria. PEG treatment induced a significant decrease in fasting plasma glucose (FPG) (effect size (ES) −0.90 mmol/l, 95%CI: −1.15–−0.66; $P=0.000$), HbA1c (ES −0.48%, 95%CI: −0.59–−0.37; $P=0.000$), fasting plasma insulin (FPI) (ES −5.12 mU/l, 95%CI: −8.99–−1.22; $P=0.010$) and HOMAi (ES −0.80, 95%CI: −1.38–−0.22; $P=0.007$), without changes of triglyceridemia, glucose load (2h-OGTT), HOMAβ, weight and BMI. Meta-regression was possible only for FPG and FPI and it revealed not significant effect of post-pre treatment IGF-1 mean difference on the pooled estimate.
Conclusions
PEG induces a significant decrease in FPG, HbA1c, FPI and HOMAi. These results suggest that PEG treatment improves glucose metabolism in acromegaly and this effect seems to be independent from disease control.

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OC13.5

Growth hormone acts in AgRP neurons to control energy expenditure during food restriction and promotes counter-regulatory responses to hypoglycemia via the ventromedial hypothalamus

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Growth hormone (GH) responsive cells are extensively distributed in central nervous system, including in neurons of the arcuate (ARH) and ventromedial nucleus (VMH) of hypothalamus, areas that control food intake, energy expenditure and blood glucose. During metabolic stresses, such as food restriction and hypoglycemia, GH secretion is stimulated and may be important to maintain survival. In the present study, we first verified that an acute GH injection stimulates food intake by increasing AgRP and NPY mRNA expression in the hypothalamus of wild-type mice. Then we generated mice lacking GH receptor (GHR) specifically in AgRP neurons or in steroidogenic factor-1 (SF1) cells, which include neurons in the VMH, in order to evaluate whether these cells mediate the effects of GH during conditions of metabolic stress. AgRP GHR KO mice exhibited similar body weight, food intake, energy expenditure, glucose tolerance and leptin sensitivity, compared to control animals. However, fasting induced a lower cFOS expression in the ARH of AgRP GHR KO than control animals. Remarkably, while control mice adapted to a 60% food deprivation period by progressively saving energy, AgRP GHR KO mice exhibited a blunted metabolic adaptation to starvation, which led to higher energy expenditure and weight loss, followed by higher T_4 production and UCP-1 mRNA expression in the iBAT. Blockage of sympathetic system with propranolol equalized the energy expenditure between the groups. In contrast, SF1 GHR KO mice exhibited similar responses to control group in food restriction, but a blunted counter-regulatory response evoked by 2-deoxyglucose (2DG) administration, indicating that GH may act in VMH cells to reverse the hypoglycemic state. In summary, GH signaling in AgRP neurons regulates the metabolic adaptations to starvation, while GH signaling in the VMH controls the counter-regulatory responses to hypoglycemia. These findings indicate a previously unidentified function of GH by acting in specific neuronal populations in order to ensure survival via the induction of appropriate metabolic responses.

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What is new in gestational and type 1 diabetes?

OC14.1

Does insulin treatment differ in their impact on placental vascular circulation in obese and non obese women with gestational diabetes mellitus?

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Objective
The present study was designed to investigate the impact of insulin treatment on placental maternal and fetal vascular circulation in obese and non-obese women with gestational diabetes mellitus (GDM).
Design and methods
One hundred and ninety two women with GDM who gave birth and underwent a placental histopathological examination at Wolfson Medical Center were included in the study: 123 women who were treated with diet (Group 1) and 69 women who were treated with diet plus insulin (Group 2). Additionally, each group was divided into two subgroups according to pre-pregnancy BMI: non-obese (A) and obese (B).
Results
Maternal vascular malperfusion lesions did not differ significantly between groups. Vascular lesions related to fetal malperfusion were significantly lower in GDM women treated by insulin and diet compared to women with diet alone ($P=0.027$). Among fetal malperfusion lesions, villous changes consistent with fetal thrombo-occlusive disease (FTOD) increased from Group 1 to Group 4 in a continuous fashion and were higher in diet treated obese women than in other study groups (0, 3.5, 13 and 26.5%, $P=0.009$). In the logistic regression analysis, insulin treatment was significantly associated with a decreased rate of villous changes consistent with FTOD (OR 0.97, 95% CI 0.12–0.80, $P=0.03$).
Conclusion
Combination of obesity and GDM increased rate of villous changes consistent with FTOD and prevalence of gestational hypertension in both treatment groups. Insulin plus diet treatment was associated with improved fetal placental vascular circulation. Prevention of obesity throughout women's childbearing age may translate to improved placental circulation and better pregnancy outcomes.

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OC14.2

Profiling of activation patterns of placental mTOR in pregnancies complicated by gestational diabetes mellitus

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The mammalian target of rapamycin (mTOR) is a serine kinase that couples energy and nutrient abundance to cell growth and is critically involved in the onset and progression of diabetes, cancer and ageing. Placental mTOR is involved in nutrient sensing and transfer to the fetus. Animal models suggest that placental mTOR is upregulated in pregnancies complicated by gestational diabetes (GDM). Our aim was to characterize expression, and cellular localization of mTOR and whether the activated fraction is affected by GDM. Our study consisted of i) GDM-mothers ($n=40$) and their offspring and ii) mothers ($n=33$) with normal pregnancies (non-GDM) and their infants. At delivery, fetal glucose was measured in cord blood and total and phospho-mTOR (Ser2448) expression were determined in placental biopsies using Western blot (WB) and immunohistochemistry (IHC) analysis. Newborn anthropometric parameters were also determined at delivery. GDM pregnant women were older (30.81 ± 4.87; 33.39 ± 5.38, $P<0.02$) and presented with higher fasting glucose levels than non-GDM (94.82 ± 19.96 mg/dl; 73.08 ± 9.77 mg/dl; $P<0.001$). No significant difference was found in birth weight or baby length between GDM and non-GDM infants. IHC analysis showed that both total and activated mTOR were predominantly expressed in trophoblasts and to a lesser extend in synciotrophoblasts, in both GDM and non-GDM placentas. GDM placentas exhibited a higher mTOR H-score compared to non-GDM ($P<0.009$), and WB analysis showed a higher phospho-mTOR signal intensity ($P=0.047$) in the same group. However, total mTOR expression was relatively increased in GDM placentas resulting in a decreased phospho/total (P/T) ratio in GDM than non-GDM placental tissues (0.95 vs 0.8, $P=0.001$). mTOR expression was increased in both GDM syncitiotrophoblasts and endothelial cells compared to non GDM ($P<0.001$) whereas a reduced signal was detected in stromal phospho-mTOR ($P=0.004$). No difference was found in trophoblasts or endothelial cells between the two study groups suggesting that activation of this kinase is tightly regulated and is relatively independent of changes in total kinase levels. The upregulation of the total mTOR levels led to a decreased P/T mTOR ratio in GDM syncytiotrophoblasts compared to non-GDM ($P<0.001$). A positive correlation was found between endothelial P/T mTOR ratio and baby length ($P=0.025$) and a negative correlation with BMI, maternal fasting glucose and fetal glucose ($P=0.005$; $P=0.025$; $P=0.026$ respectively). Placental mTOR/PmTOR expression is differentially regulated across different placental cell types and is sensitive to hyperglycaemia associated with gestational diabetes mellitus.

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OC14.3

Patrolling monocytes are activated in diabetes and provide protection to retinal vessels in the context of leukostasis

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Background
Diabetes is characterized by a prolonged latency between the onset of metabolic abnormalities and the clinical appearance of microvascular disease, consistent with the occurrence of vascular repair in the early stages. Patrolling monocytes (PMo), a subset of circulating monocytes, survey microvessels by crawling on the endothelium; their functional and biosynthetic characteristics suggest they play a role in the protection of the endothelium from vascular stress.
Hypothesis
In early diabetes, PMo adhere to retinal microvessels and exert protective functions, a potential mechanism for the latency that precedes the appearance of retinopathy.
Methods
Streptozotocin-diabetes was induced in male NR4A1-deficient mice (KO) that lack PMo, and in age-matched C57BL6/J controls (WT). To study retinal leukostasis, whole-mounted retinas from mice perfused intracardially were immunostained for CD45 (pan-leukocytic) and CD16.2 (PMo-specific) to identify and enumerate cells firmly adherent to microvessels. Retinal microangiopathy was assessed by counting acellular capillaries (AC) on retinal trypsin digests. To study their biosynthetic characteristics, RNA was isolated from circulating PMo sorted from mice after 5 months of diabetes using anti-CD45, CD11b, CD3, CD19, NK1.1, Ly6G, CD115, and Ly6C; and analyzed by RNAseq and qPCR.
Results
In WT mice, 3 months of diabetes increased firmly adherent leukocytes (Controls (C): 58 ± 23/retina, Diabetes (DM): 93 ± 18, $P<0.001$)) as well as PMo (C: 10 ± 4/retina, DM: 37 ± 6, $P<0.001$). Conversely, diabetes did not increase firmly adherent leukocytes in KO mice. AC were not increased after 4 months of diabetes in WT, nor KO mice. In WT mice, 6 months of diabetes increased AC (C: 5 ± 1/mm^2 retina, DM: 7 ± 1; $P<0.01$); the AC increase was more pronounced in KO-DM (12 ± 3) when compared to WT-DM and KO-C (5 ± 1) ($P<0.001$ vs both). RNAseq and qPCR of PMo from diabetic mice showed a pro-adhesive, anti-inflammatory, anti-apoptotic, vasculo-protective signature.
Conclusion
These data demonstrate several features of the role of PMo in diabetes including (i) more severe retinal microangiopathy in mice lacking PMo after 6 months of diabetes, (ii) increased PMo adherence to retinal microvessels at early time points of diabetes; and (iii) a vasculo-protective biosynthetic program of circulating PMo. Collectively, the findings suggest that in early diabetes PMo deliver to retinal microvessels protective/healing activities that counteract the damaging effects of diabetes. Leukostasis may thus represent, at least in part, a mechanism for healing, rather than a pro-inflammatory event as currently proposed.

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OC14.4

The variability of glycemia and the metabolic composition of brain cells in patients with type 1 diabetes mellitus

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Actuality
At present, the role of chronic hyperglycemia in type 1 diabetes mellitus (DM1) in the onset of diabetic encephalopathy has been proven. At the same time, violations in the metabolic composition of brain cells were detected in persons with DM1, estimated with the proton magnetic resonance spectroscopy (^{1}H-MRS). However, the relationship between the results of these studies has not yet been studied.
The aim
To reveal the relationship between the measures of glycemic variability and the results of ^{1}H-MRS of patients with DM1.
Materials and methods
Fifty-eight patients with DM1 at the age of 29 (25–32) years. A complete clinical and laboratory examination was carried out. Using the EasyGV© software, the measures of glycemic variability was calculated (standard deviation (SD), continuous overlapping net glycemic action (CONGA), lability index (LI), low blood glucose index (LBGI), high blood glucose index (HBGI), mean of daily differences (MODD), mean amplitude of glycemic excursions (MAGE)). The ^{1}H-MRS of the brain was performed to determine the main spectra of choline (Cho), creatine/creatine phosphate (Cr, PCr), N-acetylaspartate (NAA).
Results
The fasting glycemia in patients with DM1 was 8.6 (7.3–9.6) mmol/l, the average level of HbA1c was 8.4 (7.5-8.9)%. The measures of glycemic variability were calculated: S.D. 6.25 (3.1–7.7) mmol/l, CONGA 4.65 (3.3–7.3) mmol/l, LI 4.25 (3.3–5.1) (mmol/l)^2/hour, LBGI 3.85 (2.6–5.2), HBGI 7.75 (5.6–12.5), MODD 3.85 (2.9–5.6) mmol/l, MAGE 7.6(4.6–8.9) mmol/l. Based on the results of the ^{1}H-MRS, an analysis of the relationship with the measures of glycemic variability was carried out. A positive correlation with the parameters of Cr ($P=0.003$) and PCr ($P<0.001$) in the right hippocampus, PCr in the gray matter on the right

($P=0.036$), NAA in the gray matter on the left ($P=0.024$) was found on the CONGA. LI - negative correlation with Cho in the left hippocampus ($P=0.044$) and PCr in the right hippocampus ($P=0.023$). LBGI – positive correlation with NAA in the left hippocampus ($P=0.012$) and in white matter ($P=0.026$). MODD – positive correlation with NAA in gray matter on the left ($P=0.001$). No statistically significant correlations were found for the SD, HBGI and MAGE ($P>0.05$).

Conclusions

The study revealed a direct and inverse relationship between the measures of glycemic variability and metabolites that characterize the state of cell membranes, the neuronal integrity and metabolism of brain cells, which indicates the effect of glycemic variability on biochemical processes in the brain.

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OC14.5

Type 1 diabetes mellitus: defining the best cut-off points of arterial stiffness for predicting cardiovascular risk according to the Steno Type 1 Risk Engine

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Background

Cardiovascular disease (CVD) is the leading cause of death in persons with type 1 diabetes (T1DM). However, there are no CVD-risk prediction models for this population in widespread use and those developed from general population and type 2 diabetes have been shown to underestimate CVD-risk in T1DM. Recently, the Steno Type 1 Risk Engine (ST1RE) was developed for predicting CVD in a cohort of T1DM persons without clinical CVD. We investigate the relationship between the scores obtained from that engine and preclinical atherosclerosis measured as arterial stiffness (AS), in order to identify potential cut-off points of AS of interest in clinical practice.

Methods

One-hundred and seventy-nine persons (18–65 years old) with T1DM of >1-year duration and without clinical CVD were consecutively evaluated for: i) clinical and anthropometric data (including classical cardiovascular risk factors), ii) microvascular complications and iii) aortic pulse-wave velocity (aPWV) determined by applanation tonometry, the gold-standard for measuring AS. The ST1RE was used to estimate the 10-year CVD-risk and classify these persons into three groups: low-risk (<10%; $n=105$), moderate-risk (10–20%; $n=53$) and high-risk (>20%; $n=21$).

Results

One hundred and seventy nine persons were included (men: 50.8%, age: 41.2±13.1 years, duration of T1DM: 16 (12–23) years). As compared with subjects in the low- and moderate-risk group, those in the high-risk were older (32.5±8.3, 50.8±6.0, 60.7±6.6 years; $P<0.001$), had higher prevalence of hypertension (14.3, 37.7, 66.7%; $P<0.001$) and dyslipidaemia (36.4, 77.8, 89.5%; $P<0.001$), higher BMI (24.3±3.2, 26.6±3.8, 27.8±4.4 Kg/m^2; $P<0.001$), higher insulin resistance (eGDR: 9.2±1.8, 7.0±2.1, 5.5±1.8 mg·kg^{-1}·min^{-1}; $P<0.001$) and worst glycaemic control (HbA1c: 7.6, 8.0, 8.5%; $P<0.001$). They also had higher prevalence of microvascular complications (27.2, 43.4, 81.0%; $P<0.001$) and higher aPWV (6.4±1.0, 8.4±1.3, 10.3±2.6 m/s; $P<0.001$). aPWV was positively associated with the ST1RE score ($r=0.777$; $P<0.001$). The best cut-off point of AS for identifying subjects in the moderate-high risk group was >7.3 m/s (Se: 86%, Sp: 83%; C-statistic: 0.914 (95CI:0.873–0.95)), and for identifying those in the high-risk, > 8.7 m/s (Se: 76%, Sp: 86%; C-statistic: 0.879 (95%CI:0.809–0.948)).

Conclusions

AS was highly and positively correlated with the ST1RE score. We provide cut-off points of AS that discriminate T1DM subjects with moderate-high and high CVD-risk that could be of great interest in clinical practice.

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Guided Posters

Acromegaly

GP2

Retinal vessel abnormalities in acromegaly

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Growth hormone (GH) and insulin like growth factor 1 (IGF-I) modulate and stimulate angiogenesis and endothelial function. Excess of GH, as in acromegaly, is associated with cardiovascular morbidity and mortality, which is reversible after normalization of IGF-I and GH. Diabetes mellitus (DM) is a common comorbidity in acromegaly, but the prevalence of diabetes retinopathy in patients with acromegaly is unknown. Also, the roles of GH and IGF-I in diabetes retinopathy are not fully understood. We examined retinal vessels of 26 patients with acromegaly at diagnosis and one year after initiated treatment compared to the retina of 13 healthy controls. Fundus photographs were analyzed for vessel tortuosity, branching points and optic nerve morphology by a computer assisted mapping system. Subjective analysis for diabetes retinopathy was performed in a masked fashion. At diagnosis one patient had type-1 DM, 6 patients had type-2 DM and 6 patients had impaired glucose tolerance. The prevalence of pre-proliferative diabetes retinopathy in the patients with acromegaly and DM was 43%. Independent of diabetic status patients with acromegaly had 34.3 [30.0;39.0] (Median [interquartile range]) branching points while healthy controls had 27.0 [24.0–29.0], $P<0.001$. No difference in tortuosity of arterioles and venules or optic disc morphology was observed. The high amount of branching points remained unchanged at 1-year follow-up. In conclusion, patients with acromegaly had increased number of retinal vascular branching points without altering macroscopic vessel morphology that remained unchanged although hormone levels normalized 1 year after treatment. The prevalence of diabetes retinopathy in our patients with acromegaly and diabetes seemed to be higher than in the general type-2 diabetic population in Sweden (28.6% in 2017) according to the Swedish National Diabetes Registry.

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GP3

An insight into the putative risk factors for IGF-1/GH dichotomy during follow-up for acromegaly

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Background
Growth Hormone (GH) and insulin-like growth factor 1 (IGF-1) are the biomarkers used to assess disease activity in acromegaly. Consensus guidelines from the Endocrine Society (2014) recommend a normal (age/sex-adjusted) IGF-1 in combination with a suppressed random GH <1 µg/l for biochemical remission. However, these results are discordant in some patients. The clinical significance of the IGF-1/GH dichotomy in the follow-up of these patients is unclear and makes treatment decisions challenging.
Methods
We conducted a cross-sectional study to assess the frequency of IGF-1/GH discordance and to identify putative risk factors for its occurrence. Consecutive patients who attended our pituitary service over past 15 years were identified from the local Acromegaly Registry and medical records analysed.
Results
109 patients with acromegaly were identified (56% male, age 57.4 $\pm$ 13.6 years). Ninety-six patients (88%) underwent surgery. Fifty-six patients (51%) received radiotherapy. Fifty-six patients (51%) were on medical therapy at the time of their most recent biochemical assessment of disease status, with the majority (48 patients, 94%) receiving somatostatin analogue (SSA) therapy. Fifty-four patients (50%) had achieved biochemical remission, of whom 29 patients (54%) were not receiving long-term medical therapy. Twenty patients (18%) had both raised IGF-1 and GH >1 µg/l. Thirty-five patients (32%) had discordant IGF-1/GH results (63% ($n=22$) had high IGF-1 and normal GH (high IGF-1 discordance) and the remaining 13 patients the reverse (high GH discordance)). Age, gender, renal and liver function did not predict IGF-1/GH discordance. Higher BMI (coeff $=-2.72$, $P=0.03$) and higher GH level at diagnosis (coeff $=-2.31$, $P=0.01$) were significant negative predictors of discordance. Neither surgery nor radiotherapy were associated with an increased risk of IGF-1/GH discordance, although a high IGF-1 discordance was more prevalent post-radiotherapy (coeff $=0.43$, $P=0.02$) within the discordant group of patients. One-third ($n=16$) of patients on SSA therapy had discordant results. Being on SSA at the time of analysis was not associated with discrepant results. However, previous/current exposure to SSA was a positive predictive factor of IGF-1/GH dichotomy (coeff $=0.44$, $P=0.03$), although there was no association with treatment duration.
Conclusion
Despite the move to more robust criteria for biochemical remission of acromegaly, IGF-1/GH dichotomy remains present in around one-third of patients. In our cohort, exposure to SSA therapy, a lower BMI and lower GH level at diagnosis were significant determinants of IGF-1/GH discordance.

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GP4

Efficacy and safety of switching to pasireotide LAR monotherapy or in combination with pegvisomant in acromegaly patients controlled with combination therapy of somatostatin analogues and pegvisomant (PAPE study): a prospective, open-label 48 week study

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Background
In the core phase of the PAPE study until 24 weeks we have shown that switching to pasireotide LAR (PAS-LAR) in well-controlled acromegaly patients receiving combination therapy of somatostatin analogues and pegvisomant (PEGV), normalizes IGF1 levels in the majority of patients. PAS-LAR induced a significant PEGV sparing effect, but this was at the expense of a higher incidence of diabetes. This extension study until 48-weeks assesses the efficacy, safety and quality of life (QoL) of PAS-LAR monotherapy or in combination with PEGV by optimization of PAS-LAR and PEGV dose.
Methods
59 out of 61 patients entered the extension phase. Well-controlled patients receiving PAS-LAR monotherapy continued with the same dose, while uncontrolled patients had to restart PEGV therapy. In patients on PAS-LAR and PEGV combination therapy, the PEGV dose was titrated based on a protocol with the goal to achieve normalized IGF1 levels. At baseline, an oral glucose tolerance test (OGTT) was performed, and at each study visit QoL was assessed using the AcroQoL and PAQ3 questionnaires.
Results
At the start of the present study, median IGF1 was 0.94 $\times$ the Upper Limit of Normal (ULN) with a mean PEGV dose of 134 mg/week, and 32.8% of patients had pre-existing diabetes. At 48 weeks, median IGF1 was 0.98 $\times$ ULN, and 77% of patients achieved normal IGF1 levels with a mean PEGV dose of 64 mg/week. Cumulative PEGV dose reduction between baseline and 48 weeks was 52%. After 48 weeks IGF1 levels were normal in 93% of patients receiving PAS-LAR monotherapy, and 71% of patients receiving combination therapy. The incidence of diabetes increased to 77%. Nine patients discontinued PAS-LAR therapy, mainly due to hyperglycemia-related adverse events. Pasireotide-induced hyperglycemia was inversely related to insulin secretion during OGTT at baseline (Stumvoll, $r=-0.37$, $P=0.005$). Global AcroQoL score significantly improved (5.5%, $P<0.0001$) during treatment with PAS-LAR. The greatest improvement was observed in the physical dimension.
Conclusions
Switching to PAS-LAR monotherapy or in combination with PEGV controlled IGF1 levels in the majority of acromegaly patients after about fifty percent reduction in cumulative PEGV dose, however this coincides with a higher incidence of diabetes. The main driver of pasireotide-induced hyperglycemia seems residual β-cell function at baseline. Long-term treatment of acromegaly with PAS-LAR is a trade-off between the benefits of biochemical control and an improvement in QoL versus the burden of long-term sequelae of the pasireotide-induced diabetes.

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GP5

The importance of *MEN1* gene variants in *AIP* mutation negative FIPA patients

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Introduction
Pituitary adenomas (PAs) that occur in a familial setting account for no more than 5%, which can be part of familial tumor syndromes such as Multiple Endocrine Neoplasia type 1 (MEN1) and type 4 (MEN4), Carney Complex (CNC) or Familial Isolated Pituitary Adenoma (FIPA). The presence of two or more cases of PAs without MEN1 or CNC characteristics in the same family, enable FIPA diagnosis. Heterozygous germline inactivating mutations in the *aryl hydrocarbon receptor-interacting protein* (*AIP*) gene confer predisposition to PAs in different races in the setting of FIPAs. However, we have previously reported our cohort of FIPA patients as negative for *AIP* point mutations. Therefore, the aim of this study was to detect copy number variations (CNVs) in *AIP* and *MEN1*, and to investigate *MEN1* gene variations in this cohort.
Patients and methods
Seven families including 16 patients with FIPA diagnosis were involved in this study. Among these families, heterogenous and homogenous FIPA were composed of three and four families, respectively. All homogenous FIPA patients had somatotropinoma. Mean follow-up period of the cohort was 13 (5–40) years. Only 12 patients from these families were available for genetic analyses, who did not have hypercalcemia and other components of familial syndromes. Patients' genomic DNA were isolated from peripheral blood. All exons, exon-intron boundaries and UTR regions of *AIP* and *MEN1* genes were PCR amplified, followed by Sanger sequencing to detect point mutations. CLC Main Workbench 6.5 was used in sequence data analysis against the reference sequences NM_003977.3 and NM_000244.3 for *AIP* and *MEN1* genes, respectively. Multiplex ligation-dependent probe amplification (MLPA) was performed in CNV detection, where commercially obtained reagents and probe-mixes were used according to the manufacturer's instructions (P244-AIP-MEN1-CDKN1B, MRC-Holland, the Netherlands).
Results
In our cohort, initial screen of *AIP* gene revealed no mutations and MLPA anlaysis also showed no CNVs. Afterthan, *MEN1* sequencing exhibited novel heterozygous variants including c.1846T>A (p.*616Argext*21); rs778272737:T>C; rs972128957:C>T in 2 families having patients diagnosed with Cushing disease, non-functional PA, and acromegaly, respectively. Among them, c.1846T>A (p.*616Argext*21) is a stop codon read-through, whereas the others are 3′UTR variations. Overall, *MEN1* variation frequency was detected 15% in our cohort.
Conclusion
In the long term clinically followed-up of FIPA patients without hypercalcemia, *MEN1* gene can be of significance and screening should be offered especially to young first-degree relatives with or without MEN1 syndrome features.

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GP6

IGF-I response to pasireotide LAR treatment in acromegaly is mainly driven by somatostatin receptor subtype 2 expression

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Background
The response to first-generation long-acting somatostatin analogues (LA-SSA) treatment in acromegaly depends on the expression of the somatostatin receptor (SSTR) subtypes. In contrast to octreotide and lanreotide which preferentially bind to SSTR2, pasireotide targets multiple SSTRs, with the highest binding affinity for SSTR5. It has previously been suggested that SSTR5 expression could predict the response to pasireotide LAR (PAS-LAR) treatment in acromegaly.
Aim
To assess whether the IGF-I response to LA-SSA monotherapy correlates with the IGF-I response to PAS-LAR treatment, and whether SSTR2 and SSTR5 expression correlate with response to PAS-LAR treatment in acromegaly.
Methods
We included 52 patients from a cohort of patients that initially received LA-SSA treatment, followed by LA-SSA and pegvisomant (PEGV) combination treatment and subsequently PAS-LAR treatment during the PAS-LAR and PEGV (PAPE) study. We excluded patients that had received radiotherapy and LA-SSA therapy $\leq$ 4 months. In 14 of 52 patients, somatotroph adenoma tissues samples were available for evaluation of SSTR2 and SSTR5 expression using a semiquantitative immunoreactivity score (IRS). The response to LA-SSA treatment was defined as IGF-I levels after $\geq$ 4 months LA-SSA monotherapy. The response to PAS-LAR treatment was based on the PAPE study and defined as IGF-I levels at 24 weeks and the percentage PEGV dose reduction at 48 weeks.
Results
The mean percentage IGF-I (x ULN) reduction was similar after LA-SSA monotherapy and after PAS-LAR treatment (resp. 32.1% and 30.0%) and IGF-I levels after both treatments were directly correlated ($r=0.50$, $P=0.0002$, $n=52$). The SSTR2 IRS was inversely correlated with IGF-I levels after PAS-LAR treatment at 24 weeks($r=0.63$, $P=0.016$), but no correlation was observed with SSTR5 ($r=-0.61$, $P=0.029$, $n=14$). After exclusion of patients receiving LA-SSA pretreatment, SSTR2 IRS was correlated with the percentage PEGV dose reduction at 48 weeks after switching from LA-SSA/PEGV combination treatment to PAS-LAR treatment ($r=0.70$, $P=0.035$), while SSTR5 IRS showed no correlation ($r=0.35$, $P=0.36$).
Conclusion
In contrast to previous reports, SSTR5 expression does not predict the IGF-I response to PAS-LAR treatment, but appears to be mainly driven by SSTR2 expression.

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GP7

Familial cancer clustering in patients with pituitary adenoma

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Objective
People are at higher risk for malignancy as they get older or have a strong family history of cancer.
Aim
To collect family history of cancer in a large cohort of patients with pituitary adenomas (PA) in Outpatient clinic from years 2005–2017.
Results
Overall 46% of 1100 patients with PA had a family member affected with cancer. Breast cancer in family members was reported in 15.3% of patients with prolactinomas which was significantly higher than in families of patients with non-functioning pituitary adenomas (NFPA) (10.0%, $P=0.020$) or acromegaly (6.8%, $P=0.002$). Lung cancer in family members was reported in 12.1% of patients with prolactinomas,significantly higher than in families of NFPA patients (7.0%, $P=0.012$). Colorectal cancer in the relatives of patients was reported with any type of PA. Furthermore, patients with a positive family history of malignancy were diagnosed with PA at an earlier age than patients with a negative family history. In a separate analysis 75 (6.8%) patients with PA were diagnosed with cancer (NFPA, 38/470; acromegaly 20/221; prolactinoma 14/372, M.Cushing 3/37). Overall age incidence patterns showed higher risk at older age. Almost 50% of patients with PA who had cancer had a positive family history of malignancy.
Conclusion
These results suggest familial cancer clustering in patients with PA. In particular there is a strong association between prolactinoma and family history of breast and lung cancers, borderline with colorectal cancer. These results suggest that patients with PA and associated tumors in the family share genetic susceptibility. The results also emphasize the value of readily available family cancer history in the clinical genetic risk assessment for screening and prevention strategies in patients with PA.

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GP8

ACRONIS, a European observational study in patients with uncontrolled acromegaly who are being treated with long acting pasireotide: first interim analysis

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Acromegaly is a morbid condition mainly caused by overproduction of growth-hormone (GH) from a pituitary adenoma leading to excessive growth. Normalisation of insulin-like growth factor-1 (IGF1) is an important goal for the treatment of acromegaly. The second-generation somatostatin analog (SSA) long acting pasireotide (la-PAS) has recently been introduced for the management of patients uncontrolled by first-generation SSA. The ACRONIS study (CSOM230CIC05) will provide real-world evidence on the efficacy and safety of la-PAS in acromegaly patients from twelve countries, either already treated with monthly la-PAS for $\geq$6 months (retrospective set) or going to be treated (prospective set). Results of the first interim analysis reflecting the retrospective set are presented. The mean age of the enrolled retrospective patients (n=60) was 45.4 years; 55% female and 76.7% Caucasian. Mean time since diagnosis was 53.2 months (S.D. 54.5 months); 83.3% had previous surgery and 40.0% radiotherapy. 98.3% had taken prior medication: mainly first-generation SSAs (73.3% octreotide, 31.7% lanreotide), growth hormone receptor antagonists (53.3%) or dopamine agonists (48.3%) in mono- or combination therapy, respectively. 23.3% and 13.3% of patients were diabetic or pre-diabetic prior to la-PAS prescription, respectively. All patients were la-PAS naïve at baseline. 81.4% of patients started with la-PAS 40mg, 1.7% with 20mg and 16.9% with 60mg. After a mean duration of 8.2 months (range 6–25 months, n=59 (all patients within the retrospective set having $\geq$1 post-baseline safety assessment and with $\geq$1 dose of la-PAS)), 62.7% remained on starting dose, 32.2% were up-titrated, 5.1% down-titrated. At 6 months, IGF1 was normalised [$\leq$1 times upper limit of normal (ULN)] in 42.5%, (n=40). IGF1 normalisation and GH $<$1 ($<$2.5 µg/l) was achieved by 14.3% (21.4%) of 28 evaluable patients. These results are in line with the pivotal PAOLA study (*NCT01137682*) where 25% and 26% of patients on the 40 mg (n=65) and 60 mg (n=65) doses, respectively, achieved normalised IGF values; 15.4% and 20% respectively, achieved both IGF1 $<$1 ULN and GH $<$2.5 µg/l. The adverse events (AEs) most commonly reported were diabetes mellitus (18.6%), hyperglycaemia (13.6%), headache (10.2%) and diarrhoea (10.2%). The only reported grade 3/4 AE was headache (1.7%). The overall percentage of glucose metabolism-related AEs (33.9%) seems lower than previously reported. The safety profile of la-PAS in the ACRONIS study was consistent with its known safety profile. In conclusion, the results of retrospective ACRONIS dataset confirm the efficacy and tolerability of long-acting pasireotide in previously uncontrolled acromegaly patients in clinical practice.

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GP9

Pregnancy and acromegaly – clinical outcomes from the Irish Pituitary Network

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Acromegaly is a rare disease characterised by excessive Growth hormone (GH) production from a pituitary adenoma. Subfertility is common in acromegaly and has various aetiologies, therefore pregnancy in acromegaly is rare. We present a case series of 19 pregnancies in 13 women with acromegaly from the newly formed Irish National Pituitary Registry. Twelve women had pituitary macroadenomas, one woman had a microadenoma. The age of the women ranged from 28 to 40 years with a median of 34 years. Only 5/19 pregnancies had optimal biochemical control of acromegaly pre-conception, as defined by IGF-1 concentration in the age-related reference level and plasma GH concentration of $<$2 µg/l. There were 18 singleton pregnancies and one twin pregnancy. Four women were receiving treatment with somatostatin analogues pre-pregnancy, all 4 women discontinued therapy with the first positive pregnancy test. No woman continued somatostatin analogue treatment during pregnancy. All 4 of these pregnancies had normalisation of the plasma IGF-1 concentration in spite of the withdrawal of somatostatin analogue therapy. 7/19 pregnancies continued dopamine agonist treatment during pregnancy.

Effect of pregnancy on acromegaly; No patient had a change in visual field during pregnancy. 9/14 IGF-1 plasma concentrations that were elevated pre-conception normalized during pregnancy, with a reduction in IGF-1 seen in a further 4 pregnancies.

Effect of acromegaly on pregnancy; 17 healthy babies were born at term. 1/19 pregnancies had pre-eclampsia and an emergency C-section was performed at 32 weeks. 1/19 pregnancies (twin pregnancy) had an elective caesarean section at 35 weeks. 0/19 pregnancies developed gestational diabetes.

Our data suggests that pregnancy in women with acromegaly is generally safe, from a maternal and foetal perspective. Furthermore, biochemical control tends to improve in spite of the withdrawal somatostatin analogue therapy during pregnancy.

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GP10

Human growth hormone (GH) isoforms during oral glucose tolerance test in patients with acromegaly and in healthy subjects

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GH consists of various molecular isoforms. Most abundant is 22 kDa-GH (80–90% of total GH), followed by 20 kDa-GH (5–15% of total GH). The biological significance of 20 kDa-GH remains unclear, but its effects appear comparable to those of 22 kDa-GH. Acromegaly is characterized by chronic GH excess. Data on GH isoforms in acromegaly are scarce, but an increased 20 kDa-/22 kDa-GH-ratio (20k-ratio) has been described. Our aims were to compare the 20k-ratio in a larger cohort of treatment-naïve patients with acromegaly and healthy controls, to investigate the potential impact of BMI on the 20k-ratio and to compare the dynamics of the 20k-ratio during oral glucose tolerance test in the groups. Forty-one treatment-naïve patients with acromegaly (ACR, 13 microadenomas, 28 macroadenomas) and 137 controls (CON) were included in this study. Serum samples were collected at baseline and 30, 60, 120 and 180 min after oral glucose load (75 g). 22 kDa-GH was measured in all samples using the 22 kDa-GH-specific CLIA-IDS-iSYS (limit of quantification (LoQ) 0.05 ng/ml). In samples with 22 kDa-GH$>$0.4 ng/ml 20 kDa-GH was measured using an in-house IFMA (LoQ 0.025 ng/ml). Subjects were assigned to BMI-groups A, B, C with BMI$<$25 kg/m^2, 25–30 kg/m^2 and $>$30 kg/m^2, respectively. At baseline, 20kDa-GH was measurable in 100% (n=41) and 53% (n=73) of ACR and CON, respectively. 60 min following glucose load, 20 kDa-GH was detectable in 100% (n=41) and 31% (n=43) of ACR and CON, respectively. The baseline 20k-ratio was significantly higher in ACR (mean 20k-ratio 13.8% (range 7–26%); CON: 10.1% (range 2–18%); $P<0.0001$). There was no difference between macro- and microdenomas. In CON the 20k-ratio was lower with higher BMI (A (n=43): 11.3%; B (n=19): 8.9% and C (n=11) 7.8%; A vs B and A vs C: $P<0.05$). In ACR we could not detect a significant impact of BMI on the 20k-ratio ($P>0.05$ between all BMI-groups). Following glucose load, the mean 20k-ratio significantly increased in CON, starting at 10.1%, increasing to 12.7% and 15.5% after 30 and 60 min respectively, before returning to baseline at 180 min (10.5%). In contrast, the 20k-ratio remained unchanged in ACR. In CON the 20k-ratio was lower with higher BMI and furthermore increased temporarily after glucose load. Our data confirm that the 20k-ratio is higher in ACR, but is, unlike to CON, not regulated by BMI or acute glucose load. Thus, increased GH secretion from somatotrope adenomas seems to be associated with alterations in the regulation of isoform composition.

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GP11

Observational, multicentre study to evaluate the effectiveness in routine clinical practice of Lanreotide Autogel 120 mg at extended dosing intervals (>4 weeks) for the treatment of acromegaly: SOMACROL study

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Background
Acromegaly is usually caused by a benign pituitary tumour, with increased production of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). Treatment options include surgery, followed by pharmacological treatment with dopamine agonists, somatostatin analogues, GH receptor antagonists or radiotherapy. Treatment optimization is important to decrease the burden of this often-chronic disease on the patient.
Objectives
To evaluate the effectiveness in IGF-1 control of Lanreotide Autogel (LAN) 120 mg at extended dosing intervals (EDIs) (>4 weeks) in patients with acromegaly in routine clinical practice.
Methods
Observational, retrospective study at 38 sites (36 Spanish, 2 Portuguese) (NCT02807233). Targeted enrolment was 100 adult patients diagnosed with acromegaly, receiving LAN 120 mg at EDIs for ≥6 months, with available data on treatment start/schedule and blood GH and IGF-1 assay immediately before study visit, and no radiation therapy in the 6 months preceding. The primary outcome was the percentage of patients with normalized IGF-1 level after at least 6 months of LAN treatment at prolonged doses. Secondary outcomes included percentages of patients with GH levels ≤2.5 ng/ml or ≤1 ng/ml, and treated with EDIs of 5, 6, 7 or 8 weeks. Treatment satisfaction, quality of life (QoL) and treatment compliance were assessed.
Results
Of 114 patients included, 109 were evaluable. Mean (±s.d.) age was 59.1 (±13.2) years. 69.7% had tumour resection performed on average 12.8 (±9.4) years ago. 25.7% received radiotherapy on average 17.9 (±9.4) years ago. 83.5% had comorbidities, with hypertension the most common (64.4%). 77.1% had concomitant medication for conditions besides acromegaly. LAN had been the first-line pharmacological treatment for 67.0% of the patients. 91.7% had normalized IGF-1 values. 80.6% had GH levels ≤2.5 ng/ml, and 58.3% had levels ≤1 ng/ml. The EDIs most commonly used in routine clinical practice were 8 weeks (35.8%) and 6 weeks (37.6%). AcroQoL questionnaire showed that patients had a medium level of physical [59.7 (±24.5)] and psychological [64.9 (±20.1)] QoL. TQ10M-9 questionnaire revealed that patients were satisfied with treatment [75.1 (±16.6)], and considered it effective [70.6 (±18.7)] and convenient [69.1 (±17.6)]. General therapeutic compliance during preceding 6 months was 94.5%.
Conclusions
LAN 120 mg at EDIs (>4 weeks) during at least 6 months provided IGF-1 control in more than 90% of patients with acromegaly, with good levels of treatment satisfaction and compliance.
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GP12

Cumulative effects of growth hormone and insulin-like growth factor-1 exposure on cardiovascular, cerebrovascular and metabolic co-morbidities in acromegaly patients

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Background
Acromegaly is characterised by growth hormone (GH) and insulin-like growth factor (IGF-1) hypersecretion. The disease is associated with increased cardiovascular, cerebrovascular and metabolic co-morbidities, resulting in excess mortality. A target GH <1 μg/l and normalised IGF-1 values correlate with mortality risk reduction. However, there is lack of consensus over which biomarker, GH or IGF-1, better predicts increased morbidity and/ or mortality.
Objective
To investigate the relationship between surrogates of vascular risk and disease activity and assess the impact on cardiovascular/cerebrovascular outcomes.
Methods
Medical records of 109 patients, identified from our local Acromegaly Registry over past 15 years, were retrospectively examined (56% male, age at diagnosis 42.6±14.0 years, 1612 person-years from diagnosis).
Results
Fifty-four patients (50%) were in biochemical remission; 35 (32%) had discordant IGF-1/GH results and 20 (18%) had elevated IGF-1 and GH>1 μg/l at last biochemical assessment of disease status. Prevalence of vascular risk factors: Hypertension – 46 patients (42%); insulin resistance (IR) – 29 patients (27%); dyslipidaemia – 32 patients (29%). Nearly half (30/61) of patients with recently documented weight were obese (BMI>30 kg/m^2). The rates of hypertension (16/35, 46% vs 10/20, 50%) and IR (8/35, 23% vs 11/20, 55%) were higher in the discordant and uncontrolled groups. The presence of IR was predicted by a higher BMI (coeff=0.438, P=0.006) and older age at diagnosis (coeff=2.03, P=0.016). Longer duration of active disease also positively correlated with IR (coeff=0.947, P=0.001), although GH/IGF-1 measurements displayed no association. No significant correlation was demonstrated between age, gender and disease activity with hypertension, dyslipidaemia nor obesity. Sixteen patients (15%) had a history of cardiovascular /cerebrovascular disease (CVD/CVA), with the majority arising in the discordant GH/IGF-1 group (8/16, 50%), although no significant correlation was identified with disease activity. Dyslipidaemia was a positive predictive factor of CVD/CVA (coeff=0.42, P=0.018) whilst the other vascular risk factors were independent. A higher GH level at last biochemical assessment was also associated with a higher cardiovascular risk (coeff=0.599, P=0.010). No association was found between CVA and radiation therapy.
Conclusion
Patients with acromegaly have an unfavourable metabolic profile, in particular dyslipidaemia and insulin resistance which increase cardiovascular risk. In our cohort, high ambient GH level was a reliable biomarker for development of adverse cardiovascular events. In cases of GH/IGF-1 dichotomy, we recommend adjuvant medical treatment, especially in high GH discordance, to lower GH excess.
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Adrenal Case Reports

GP13

Adrenal schwannoma presenting as an adrenal incidentaloma in a pregnant woman

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Introduction
Adrenal schwannomas are very rare tumors that are difficult to diagnose properatively. They represent only 1–3% of all retroperitoneum masses.
Case report
A 30-year-old woman was referred to the outpatient to evaluate an adrenal mass incidentally found on abdominal ultrasonographic images obtained for self-limit abdominal pain. Her medical and family histories were unremarkable. Clinically asymptomatic, only referred amenorrhea for two months. Physical examination showed BMI 20 kg/m^2, blood pressure 125/75 mmHg, pulse rate 88 lpm. The rest of the exploration was within normal. The patient's endocrinologic data were as follows: Plasma metanephrine 34 pg/ml (<65), plasma normetanephrine 52 pg/ml (<169), urinary metanephrine 240 μg/24 h (<341), urinary normetanephrine 189 μg/24 h (<444), urinary vanillymandelic acid 2.8 mg/24 h (< 9), Cromogranine A <5 ng/ml, DHEA-S 0.8 mcg/ml (<4), Testosterone 0.8 ng/ml (<0.48), urinary free cortisol 124.1 μg/24 h (<176), Aldosterone 217 pg/ml (< 160), PRA > 11.5 ng/ml per hour (<5.7), LH 0.1 mUI/ml, FSH 0.1 mUI/ml,

Estradiol 1502 pg/ml, Progesterone 39.9 ng/ml, hCG 161250 mUI/ml (compatible with pregnancy of 6–12 weeks). Ultrasonography of the abdomen demonstrated a well-circumscribed hypoechoic mass with cystic and necrotic components that measured 32×27 mm, dependent of the right adrenal gland. MRI without gadolinium (2nd trimester) showed a 40×32 mm heterogeneous adrenal mass with necrotic and cystic components, located in the right adrenal gland, low intensity on T1-weighted images and high intensity on T2-weighted images, suggestive of pheochromocytoma as the most likely option, without being able to rule out an adrenal carcinoma. With these results we request a gynecological examination; which showed a 6-week gestation. After much deliberations, a laparoscopic adrenalectomy was performed under the suspicion of a malignant tumor or a non-functioning pheocromocytoma, in week 22 of gestation. Microscopically, the surgial specimen showed a tumor formed by fusiform cells, without atypia, with a swirling pattern and degenerative areas.Tumor cells express s100 protein and the proliferative index ki67 was 1%. The diagnosis was an ancient adrenal schwannoma. After surgery, pregnancy and delivery developed normally.

Conclusions

Adrenal swchannomas are extremely rare tumors, specially during pregnancy. Surgical resection is the primary means of management of adrenal schwannomas, as it is not possible to distinguish the schwannoma from malignant entities or pheocromocithoma simply base on imaging. In pregnant woman, like our patient, adrenalectomy should be performed in the second trimester, between weeks 12 and 24 of gestation.

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GP14

Sporadic paraganglioma and the importance of genetic screening

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Introduction

Paragangliomas are neuroendocrine tumors derived from the extra-adrenal paraganglionar system and are closely related to pheochromocytoma. About 50% are associated with genetic syndromes.

Case report

We report a case of a sporadic paraganglioma incidentally found in a 30-year-old man, with no family or personal history of interest, in the context of abdominal pain study where a mass of 5×3×3 cm is detected in the abdominal aorto-cava area ultrasound. Scintigraphic study showed a focal increase of MIBG uptake in the level of anterior planes of the right paraumbilical abdominal region without any other pathological findings. Urinary cathecolamines and metanephrines were normal. A fine needle aspiration citology was made and confirmed the diagnostic of paraganglioma. Clinical study was completed with 24-hour ambulatory blood pressure monitoring, being diagnosed with arterial hypertension and starting treatment with labetalol 100 mg per day. Finally the patient underwent by right retroperitoneal lumbotomy. Histological examination revealed a paraganglioma that reaches focally the edge of the main surgical piece with no evidence of tumor in five lymph nodes. Clinical evolution was favorable with normalization of blood pressure without requiring pharmacological treatment and with negative morphological study during follow-up. Despite not having a family history of known pheochromocytoma/paraganglioma and given the age of the patient, a genetic study was performed and confirmed c.591del/p.Ser198Alafs*22 mutation in the SDHB gene. It has been described in the Mediterranean population that individuals with mutations in SDHB have a probability of developing the disease in 8, 18 and 30% at 40, 60 and 80 years respectively. Given the dominant nature of the disease, it is convenient to realize a genetic study on other relatives who are at risk of being carriers of the disorder and who do not yet know their condition. Besides, carriers of a germline mutation in SDHB have a probability around 45% of developing metastasis.

Conclusions

The genetic analysis of apparently sporadic cases reveals that up to 25% of them have a genetic mutation. Therefore, genetic screening allows early identification of the family members carrying the same mutation and carrying out the pertinent study and follow-up. In our case, despite the favorable evolution of the patient and given the greater malignant potential of this mutation, we will maintain a long-term morphological follow-up.

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GP15

Etomidate for the management of severe hypercortisolaemia in different clinical scenarios – a case series

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Cushing's syndrome is associated with life-threatening complications, as well as high rates of perioperative mortality and morbidity. Authors present clinical scenarios, in which one should consider the usage of intravenous etomidate as an accurate, safe and effective drug for hypercortisolaemia.

Case 1

23-year-old female with severe Cushing's syndrome due to metastatic adrenocortical carcinoma was admitted to the Department of Endocrinology. She presented with uncontrolled diabetes and hypertension, hypokaleamia, hypocalcaemia and symptoms of an upper respiratory tract infection. Post-adrenalectomy, mitotane, ketoconazole, metyrapone and spironolacton were used to control the disease with poor effect. Her cortisol levels persisted at 90–128 μg/dl, so she was put on the continuous intravenous infusion of Hypnomidate with fast improvement in her clinical condition. She was able to start chemotherapy after one week of etomidate treatment. 8 days later, she was admitted again with chemotherapy-induced leucopenia and diarrhea with electrolyte disturbances. Etomidate infusion was introduced again, until her blood parameters and gastrointestinal symptoms improved.

Case 2

45-year-old male with the history of recently diagnosed diabetes, refractory hypokalaemia and mild cushingoid features, was admitted to the Department of Endocrinology. Hormonal evaluation revealed ACTH-dependent Cushing's syndrome. Treatment with ketoconazole was started. In the sixth day of ineffectual oral therapy, the patient's clinical state deteriorated with fever, spinal pain and exhaustion, due to Staphylococcus aureus sepsis. Cortisol level reached 160 μg/dl, so Etomidate-Lipuro was given intravenously. With short breaks, the infusion was carried on for 50 days. During that time, diagnostic process was completed with the final diagnosis of pituitary corticotropinoma and subsequent effective neurosurgical intervention.

Case 3

66-year-old female with ectopic Cushing's syndrome due to metastatic lung carcinoid tumour was referred to the Department of Endocrinology with severe hypercortisolaemia, decompensation of diabetes, deep hypokalaemia and mood disorders. She already had her left adrenal removed 3 months ago. As she was mentally and physically unstable, she was put on Etomidate-Lipuro infusion with an immediate improvement in her status. The course of her hospitalization was complicated with cephalic vein thrombosis, candidiasis, sepsis and post-antibiotic enterocolitis pseudomembranacea, until she was able to undergo complete adrenalectomy (after 58 days of etomidate), without further complications.

Conclusions

In doses far lower than those used for anesthesia, etomidate works as a useful cortisol-lowering therapy in patients intolerant of or unable to take oral medications. Also if urgent medical intervention is necessary, clinicians should be aware of such therapeutical option.

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GP16

Pheochromocytoma associated with cutaneous and uterine leiomyomatosis and renal cancer in a patient with a germline mutation in the FH gene

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Introduction

Most of pheochromocytomas (PCC) and paragangliomas (PGL) are sporadic. However, up to 40% of them have an inherited origin due to germline mutations in at least 15 known PCC/PGL genes, being the VHL and SDHx genes the ones most frequently affected. The fumarate hydratase (FH) is a Kreb's cycle enzyme encoded by the FH gene.Its inactivating mutations increase intracellular levels of fumarate, leading to tissular pseudohypoxia and transcription of genes involved in tumor growth, thus acting as a tumor-supressor gene. Germline heterozygous mutations in the FH gene have been associated with the hereditary

leiomyomatosis and renal cell cancer syndrome (HLRCC).More recently, FH mutations have been also related to rare cases of inherited PCC/PGL with an apparently high predisposition to malignant disease. However, none of the reported cases combined PCC/PGG and HLRCC.

Case report

In April 2007 a 44-year-old woman with a previous history of hysterectomy due to uterine myomatosis and with family background of uterine myomatosis in her mother, looked for medical attention because of frequent episodes of palpitations, headache, facial flushing and dizziness, associated with elevation of blood pressure. Laboratory tests showed increased levels of plasma and urine normetanephrine and norepinephrine.Abdominal CT scan revealed a 1.3× 1.3×9.6 cm predominantly cystic mass in the left kidney and a 9 cm left adrenal tumor with peripheral enhancement after contrast administration and a central area of necrosis. After pre-surgical preparation, adrenalectomy and ipsilateral nephrectomy were done, with clinical improvement and normalization of urinary normetanephrine and norepinephrine. Pathological examination confirmed a 9.5 cm pheochromocytoma with foci of necrosis without vascular invasion and a 10 cm Fuhrman's grade 4 renal carcinoma with extensive cystic degeneration and tubulo-papillary pattern. A preliminary genetic study was negative for RET, VHL and SHDB genes, but a further investigation with a genetic panel covering 14 PCC/PGG genes, showed a splice site mutation in the FH gene (c555 + 1G > A). This mutation had been previously reported in a Spanish family with uterine and cutaneous leiomyomatosis.Clinical reexamination of the patient revealed pink papules up to 2 cm of diameter on the forearms and trunk, whose biopsy confirmed to be cutaneous leiomyomas.Follow-up chest/abdomen CT scans and ^{123}I-MIBG SPECT have ruled out local recurrence or metastases.

Conclusions

Subjects carrying germline pathogenic mutations of the FH gene are at risk of developing both PCC/PGG and HLRCC.Both conditions should be routinely screened once diagnosis has been established.

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GP17

A rare cause of endocrine hypertension

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Introduction

Just-glomerular tumours (reninomas) are rare causes of secondary hypertension (HT). They typically present with difficult to manage-HT, hypokalemia, hyperreninemia and secondary hyperaldosteronism. They are usually small lesions (< 1 cm) and are more common in adolescents or young adults. Despite being rare, they should be considered in the diagnostic approach of secondary HT, as it they are a potentially curable cause.

Case report

Female patient, 45 years old, with personal history of difficult to manage-HT associated with hypokalemia since age 35, medicated with perindopril/amlodipine, metoprolol and spironolactone. She was sent to our department and, after suspension of spironolactone and correction of hypokalemia, we confirmed secondary hyperaldosteronism, with aldosterone of 44.3 ng/dl (4–28 ng/dl) and renin > 1000 mIU/ml (4.4–46.2 mIU/ml). She performed an abdominal CT, which identified a heterogeneous nodule located in the middle third of the right kidney, with 37 mm; renal arteries had normal diameter. Partial nephrectomy was performed afterwards and histological analysis confirmed the diagnosis of reninoma, with 27 mm of diameter. After surgery, the patient had normal levels of aldosterone (9.2 ng/dl) and renin (1.20 mIU/ml). She remains without any antihypertensive medication and underwent an ambulatory blood pressure monitoring for 24 h, which confirmed the normalization of blood pressure.

Conclusion

Reninomas are very rare tumours and a potentially curable cause of endocrine hypertension. They are usually benign and its diagnosis should be considered in patients with difficult to control-HT, hypokalemia and secondary hyperaldosteronism, in whom renovascular or parenchymal disease has been excluded. In this case, considering the surgical indication proposed by the urologist regardless of the tumor's functional behavior, the high clinical suspicion and the patient's comfort, we chose not to suspend the antihypertensive medication, except for spironolactone. Surgical resection of the tumor is the treatment of choice and leads to normalization of blood pressure.

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GP18

Bilateral testicular masses and adrenal insufficiency in a young adult: is congenital adrenal hyperplasia the only possible diagnosis?

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Testicular adrenal rest tumours (TARTs) are benign tumours deemed to originate from ectopic adrenal cells that descend with the testes during fetal development. These cells grow under chronic ACTH stimulation, typically in patients with congenital adrenal hyperplasia (CAH). TARTs have also been rarely described in other conditions characterised by chronically elevated ACTH, such as autoimmune primary adrenal insufficiency (PAI). These are benign lesions, but could be misdiagnosed as Leydig cell tumours (LCT). X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder of beta-oxidation that results in accumulation of very long chain fatty acids (VLCFA) in various tissues. The phenotypic spectrum is heterogeneous, with different age of onset and severity of neurological involvement. More than 50% of patients have PAI, but only 10% have ALD-associated PAI without neurological involvement, this usually presenting before the age of 10. A 19-year-old young male was referred to our Unit for assessment of elevated ACTH. He had previously undergone bilateral enucleation of presumed LCTs at the age of 8, and follow-up scans later showed persistent bilateral lesions compatible with TARTs, stable through the years. His past medical history was otherwise unremarkable, and clinical examination was normal. We also performed a semen analysis, which showed asthenoteratospermia. In order to exclude CAH, an androgen profile was requested, which showed a slightly elevated 17OHP (2.8 ng/ml) and normal androstenedione, DHEA-s and testosterone. An ACTH stimulation test was performed, which showed insufficient response of cortisol (6.7 μg/ml at 30′), but also a flat response of 17OHP to stimulus (2.8 ng/ml at 60′), confirming the diagnosis of PAI but ruling out CAH. Aldosterone and renin were normal, indicating a preserved mineralocorticoid production. Adrenal antibodies were negative. A serum VLCFA panel was consistent with X-ALD, with subsequent gene testing confirming the diagnosis (mutation c.346G > A of *ABCD1* gene). A brain MRI was normal, supporting the diagnosis of Addison-only ALD.

Conclusion

Adrenoleukodystrophy should always be considered in any case of primary adrenal insufficiency diagnosed in young males, even when the clinical picture could suggest a different aetiology. We expect to confirm that the testicular lesions are indeed TARTs (a follow-up ultrasound is due to be performed, and histological revision of the previously resected testicular lesions is awaited) - this would be the first case ever reported of TARTs in a patient with ALD-associated PAI. This could warrant additional investigation for a potentially reversible cause of infertility in these patients.

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GP19

Nonclassical congenital adrenal hyperplasia in a young patient with Type 1a Glycogen storage disease: is there a novel link between glucose metabolism and adrenal steroidogenesis?

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Introduction
Glycogen storage disease type Ia is a rare genetic disorder that develops due to deficient activity of the enzyme glucose 6-phosphatase and manifests clinically early in life with hypoglycemia and failure to thrive, as well as with organ dysfunction, due to excess glycogen accumulation, including hepatomegaly and kidney dysfunction. Endocrine manifestations are commonly encountered in these patients. However, due to their rarity, endocrine dysfunction has not been well-acknowledged and studied.
Case presentation
A 17-year old girl with glycogen storage disease type Ia diagnosed in neonatal life, presented with oligomenorrhea since menarche (14 years of age). Clinical examination revealed a normally grown girl, Tanner Stage V, with BMI = 24.2 kg/m^2 and normal blood pressure (120/70 mmHg). No signs of hyperandrogenism or acanthosis nigricans were noticed. A full hormonal workup revealed normal thyroid function, increased LH/FSH ratio, normal testosterone and elevated levels of 17-OH progesterone (17-OH prog = 5.04 ng/ml). Additionally, the patient displayed elevated levels of aldosterone, with suppressed plasma renin activity, leading to an aldosterone-to-renin ratio of 36. Due to the above findings, the patient was submitted to adrenocorticotropic hormone (ACTH) stimulation test, which showed adequate excretion of cortisol, along with increased levels of 17-OH progesterone and androstenedione following stimulation. The renin-aldosterone axis was further assessed with IV saline infusion test, which, however, was not diagnostic due to technical difficulties. In a 24-hour urine collection, an increased excretion of potassium, with normal potassium levels in the plasma, was noticed. Consequently, due to the possibility of a non-typical form of congenital adrenal hyperplasia (NCAH) and a coexisting subclinical hyperaldosteronism, genetic testing to analyze both CYP21A and CYP11B1 genes from genomic DNA of the patient was undertaken. The molecular testing results revealed 4 variations in homozygosity and 1 in heterozygosity at the CYP21A2 gene, as well as 1 variation in heterozygosity at the CYP11B1 gene, which, however, are not reported in all databases reviewed and their clinical significance remains unknown. The results of genetic testing of both parents, which will illuminate further this case, are pending.
Conclusions
The clinical and hormonal phenotype of NCAH in a girl with glycogen storage disease type 1A, in combination with a genomic analysis revealing mutations in both CYP21A2 and CYP11B1 genes, pose a question whether there is a novel link between these two clinical entities.

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GP20

Cushing's syndrome revealing carney complex due to novel PRKAR1A mutation

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Introduction
Carney complex (CNC) is a rare multiple neoplasia syndrome characterized by pigmented lesions of the skin and mucosa in association with various endocrine and non-endocrine tumors. The disease can be inherited in an autosomal-dominant fashion or occur sporadically due to novel mutations in the PRKAR1A gene. Primary pigmented nodular adrenocortical disease (PPNAD) is a common endocrine manifestation of CNC.
Case description
A 20-year-old woman with bilateral avascular necrosis of the femoral heads was referred for suspected Cushing's syndrome. She reported a 34 kg weight gain, significant stretch marks, rounding of the face, and worsening anxiety over the past year. Physical examination revealed facial plethora, dorsal fat pad, truncal obesity, and multiple striae. In addition, she had several hyperpigmented macules on her lips. Biochemical investigation showed 24 hour urine free cortisol of 22 μg/24 h (reference range 3.5–45 μg/24 h) and non-suppressible serum cortisol levels of 9.5 μg/dl (262 nmol/l) and 13.0 μg/dl (359 nmol/l) following 1 and 8 mg overnight dexamethasone administration respectively. Adrenocorticotrophic hormone (ACTH) was undetectable at <5.0 pg/ml (reference range 10–60 pg/ml), suggestive of ACTH independent Cushing's syndrome. Non-contrast CT imaging of the abdomen failed to identify an adrenal mass and was read as normal. On closer examination, however, there appeared to possible bilateral adrenal micronodular disease present. She subsequently underwent bilateral laparoscopic adrenalectomy, and pathology confirmed PPNAD. Genetic testing revealed a novel frameshift pathogenic variation in the PRKAR1A gene, consistent with a Carney complex diagnosis. Screening echocardiogram and thyroid ultrasound did not reveal cardiac myxoma or thyroid disease. Femoral head necrotic lesions resolved without the need for orthopedic intervention.
Discussion
We present a case of Cushing's syndrome revealing CNC due to a novel inactivating PRKAR1 mutation. PPNAD, in association with CNC, should be considered in the differential for ACTH independent Cushing's syndrome, especially when adrenal imaging appears normal.

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GP21

The importance of the follow-up after bilateral adrenal adenomectomy for Cushing's syndrome

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Introduction
We report a case of adrenal tumor recurrence after bilateral adenomectomy for Cushing's syndrome.
Case report
A 44-year-old female diagnosed in June 2014 with Cushing's syndrome caused by bilateral adrenocortical tumors, which were identified by an abdominal CT (right tumor-2.6/ 2/1.8 cm, left tumor-3/2/2 cm). At presentation, the patient had typical signs and symptoms of hypercortisolism and complications such as: arterial hypertension, dyslipidemia, severe osteoporosis with fragility rib fracture. Biological: an altered circadian cortisol rhythm (0800 h cortisol-19 μg/dl, 1100 h cortisol-28 μg/dl), decreased ACTH (ACTH < 5 pg/ml) and unsuppressed cortisol by either low and high doses of dexamethasone (cortisol 24.3 μg/dl after 1 mg DXM and 16.6 μg/dl after DXM 2×2, respectively). As adrenal venous sampling showed that the right adrenal mass has secreted more cortisol than the left one, we decided to perform right adrenal adenomectomy (histopathological result showed nodular adrenal hyperplasia). The postoperative follow-up revealed persistent hypercortisolism and left adrenal adenomectomy was performed as well (anatomopathological examination confirmed adrenocortical adenoma). We initiated the replacement therapy with Hydrocortisone 25 mg/day for the functional adrenal insufficiency. The patient was monitored every 6 months, but there were no significant changes in clinical, hormonal or CT characteristics until the last re-evaluation (October 2017) when the CT scan performed showed a tumoral recurrence of 20/13 mm size in the extern arm of right residual adrenal gland and, also multiple hypoenhancing images dispersed in the sixth segment of the liver, as well as several pulmonary nodules in the lower part of both lungs. The hormonal investigations were unaffected, so the patient continued the glucocorticoid replacement therapy. These findings raised the need for extensive evaluation for digestive malignancy and the adrenal neoplasm could not be excluded as well.
Conclusion
The follow-up is mandatory in patients with nodular hyperplasia, as adrenal adenomectomy may not solve the problem and recurrences may occur even after several years.

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Adrenal Clinical

GP22

Hypoadrenalism in advanced HIV: a pilot study

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Background
Addison's disease is probably under-diagnosed in South Africa, given that the prevalence is considerably lower than reported in Western countries (Chabre O

2017); this is important as patients may be dying from a highly treatable condition. In addition, large populations of HIV and tuberculosis infected patients in South Africa may have some symptoms erroneously attributed to these conditions, rather than Addison's disease. We determined the prevalence and aetiology of Addison's disease among hospitalised HIV-infected patients.

Methods

HIV-positive patients with a CD4 count of less than 100 cells/mm^3 and concurrent opportunistic infection, who were admitted to a medical ward were assessed with simultaneous early morning plasma cortisol and ACTH analysed by immunoassay (Roche Cobas 6000 platform). Where the basal cortisol was less than 550 nmol/l, a 250 μg *Synacthen* test was performed. Patients were excluded if they had received any steroids in the three months prior to enrolment.

Results

A total of 60 patients (23 males and 37 females) were evaluated in this interim analysis. The age median and interquartile range at presentation was 36.0 (32.0–40.0) years. The median duration of feeling unwell, prior to admission was 26.0 (14.0–60.0) days. Intercurrent pulmonary tuberculosis (TB) was diagnosed in 60% of these patients and 11 (18%) were already on antiretroviral treatment. Despite being severely ill, 37 (61%) had a basal cortisol of less than 550 nmol/l and the basal ACTH was elevated in 12%, whereas in the remainder it was in the reference range. A 250 μg *Synacthen* test was performed in 21 (35%). Of these four patients had an inadequate cortisol reserve at 30 min (<550 nmo/l), of whom three patients had central hypoadrenalism and one patient had primary hypoadrenalism, suggesting an overall prevalence of hypoadrenalism in this group of 6.7%. The median maximal cortisol following a *Synacthen* test was 697.0 (558.0–793.0) nmol/l, with at least five additional patients demonstrating an increment of less than 200 nmol/l.

Conclusions

In this severely ill patient group, at least 8% demonstrated relative adrenal insufficiency, which could contribute to the future high mortality Preliminary data indicate a relatively low prevalence of overt hypoadrenalism (6.7%), but since it is a life-threatening illness it warrants screening in the future.

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GP23

Nicotinamide Nucleotide Transhydrogenase as a novel treatment target in adrenocortical carcinoma

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Adrenocortical Carcinoma (ACC) is an aggressive malignancy with poor response to chemotherapy. Here we evaluated a potential new treatment target for ACC, focusing on the mitochondrial NADPH generator Nicotinamide Nucleotide Transhydrogenase (NNT). NNT has a central role within mitochondrial antioxidant pathways, protecting cells from oxidative stress. Inactivating human NNT mutations result in congenital adrenal insufficiency. We hypothesized NNT silencing in ACC cells will induce toxic levels of oxidative stress. To explore this hypothesis, we transiently knocked down NNT in NCI-H295R ACC cells. As predicted, this manipulation increased intracellular levels of oxidative stress; this resulted in a pronounced suppression of cell proliferation and higher apoptotic rates, as well as sensitization of cells to chemically induced oxidative stress. Steroidogenesis was paradoxically stimulated by NNT loss, as demonstrated by mass spectrometry-based steroid profiling and real-time PCR. Pharmacological inhibition of antioxidant pathways downstream of NNT also displayed potent anti-tumour effects in vitro. Next, we generated a stable NNT knockdown model in the same cell line to investigate the longer-lasting effects of NNT silencing. After long-term culture, cells adapted metabolically to chronic NNT knockdown, restoring their redox balance and resilience to oxidative stress, although their proliferation remained suppressed. This was associated with higher rates of oxygen consumption. The molecular pathways underpinning these responses were explored in detail by RNA sequencing and non-targeted metabolome analysis. Transient NNT knockdown induced major alterations in core molecular pathways that control cellular proliferation and viability, and had far-reaching effects on cell metabolism. Stable knockdown was associated with changes in protein processing in the Endoplasmic Reticulum and up-regulation of polyamine synthesis, which may facilitate the observed adaptation to oxidative stress. Our study provides the first pre-clinical evidence of the therapeutic merit of antioxidant targeting in ACC as well as illuminating the long-term adaptive response of cells to oxidative stress.

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GP24

Germline CYP2W1*6 polymorphism is a new predictive marker of sensitivity to mitotane treatment in advanced adrenocortical carcinoma: a multicenter European study

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The cytochrome P450 2W1 (CYP2W1) is an orphan enzyme able to activate anticancer pro-drugs and to metabolise endogenous substances as fatty acids and lysophospholipids. Aim of the study was to evaluate the frequency of CYP2W1 polymorphisms in patients with adrenocortical carcinoma (ACC) and correlate it with the sensitivity to mitotane, which represents the only approved drug for the treatment of advanced ACC.

Methods

A multicenter retrospective study including 182 Caucasian ACC patients (F/M = 121/61) treated with mitotane monotherapy in adjuvant ($n = 103$) or palliative ($n = 79$) setting from six centers belonging to the European Network for the Study of Adrenocortical Tumors (ENSAT) was performed. DNA was extracted from whole-blood and three CYP2W1 polymorphisms were genotyped by PCR and sequencing: CYP2W1*2 (p.A181T), CYP2W1*5 (p.Q482H) and CYP2W1*6 (p.P448L). Clinico-pathological data and an accurate follow-up during mitotane monotherapy were annotated. The response to therapy was evaluated by time to progression (TTP) from the start of mitotane treatment.

Results

The frequencies for allele*2 and *6 were in Hardy-Weinberg equilibrium. CYP2W1*5, which is only reported in non-Caucasian population, was not found. We didn't observe any correlation between the presence of CYP2W1*2 allele and clinical outcome. However, considering the incompletely resectable, metastasized or recurrent ACC, patients with CT/TT genotype at CYP2W1*6 showed a worse response to mitotane (median TTP 3 *vs.* 8 months, $P = 0.019$, HR 1.77) and a higher rate of progressive disease (71% *vs.* 41%; $P = 0.018$, chi-square = 5.57) than the wild-type group. Looking at mitotane plasma levels, 76% of CT/TT patients did not reach the target therapeutic levels (14–20 mg/L) in comparison to 52% of wild-type group ($P = 0.052$, chi-square = 3.794). No relevant impact of CYP2W1*6 was observed in patients treated with mitotane in adjuvant setting.

Conclusion

We demonstrated that ACC patients with advanced disease and CT/TT genotype at CYP2W1*6 had a worse response to mitotane treatment. Thus, this study suggests a possible use of germline CYP2W1*6 polymorphism as a new predictor marker of response to mitotane treatment in advanced ACC, avoiding useless drug administration leading to toxicities for patients.

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GP25

Metabolic fingerprints after Cushing syndrome cure

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Introduction
Active hypercortisolism of Cushing syndrome (CS) determines major changes in the plasticity and function of metabolic key target tissues as the adipose tissue (AT). Persistence of target tissue altered metabolic memory after the cure/remission of Cushing syndrome is still at debate as clinical observational studies are limited due to confounder factors both in endogenous as exogenous CS. We postulate that after remission of hypercortisolism, adipose tissue (AT) present persistent deregulations for a long time after the cure of CS contributing to the maintaining of a metabolic syndrome-like phenotype and an increased cardiovascular risk. The aim of this study was to investigate the metabolic phenotype and the adipose tissue after the cure of CS employing an established reversible CS animal model (doi: 10.1073/pnas.1323681111).
Methods
Prospective study in animal C57BL/6 mice with reversible CS studied in active hypercortisolism and after the reversion to eucortisolism. Groups: j). Mice with active CS (ACS) induced by oral chronic treatment with glucocorticoids (GC); (jj). Mice with obesity induced by hypercaloric diet (HCD); (jjj). Controls (CTR). Mice from group's j and jj received treatment (GC *vs.* HCD) during 5 weeks (W). All animals were metabolically and hormonal phenotyped at treatment end (at 5W) and at 15W. Adipose tissue distribution (MRI), plasticity (histology) and function (RNAseq, rt-PCR, cytokine arrays) were analyzed in all groups.
Results
GC treated mice presented after 5W of treatment the complete CS phenotype. Reversible CS mice (RCS) presented at 15W after the end of the active treatment no significant changes in body weight but an increase in white adipose tissue (WAT) ($P<0.005$), and marked insulin resistance (HOMA-IR: $P<0.05$ and ITT: $P<0.01$) as respect to CTR and HCD. WAT of RCS presented low turnover, hypertrophic adipocytes ($P<0.05$). Heat map, PCA and t-SNE analysis and the persistence of 488 up- and 388 down- regulated genes between active ACS and RCS indicate profound alterations of WAT in RCS mice. Genes validation, pathway and adipocytokines analysis are in process.
Conclusion
This is the first study in a murine animal model reporting the persistence of an altered metabolic phenotype marked by insulin resistance and changes in the adipose tissue plasticity after cure of CS.

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GP26

Segmental adrenal venous sampling may give a key to solution about the debate of cosyntropin stimulation or not

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Background
Adrenal venous sampling (AVS) is critical to differentiate unilateral primary aldosteronism (PA) subtype. However, there are large discrepancies between institutions in the diagnostic criteria of AVS. Especially, the most major debate is in whether cosyntropin stimulation should be used for localization diagnosis or not. Segmental AVS (S-AVS) is a refinement of central AVS (C-AVS) in which samples are taken from the tributaries of the central adrenal veins allowing the identification of the intra-adrenal aldosterone secretion in far more precise fashion.
Objective
To examine C-AVS data before and after cosyntropin by those of S-AVS.
Methods
The results of both C-AVS and S-AVS procedures in all 248 cases (133 APA and 115 BHA) performed in our institution were interpreted with diagnostic criteria of lateralized index (LI) by C-AVS. All of the APA cases underwent unilateral laparoscopic adrenalectomy based on the S-AVS findings, and were reconfirmed by pathologically and by postoperative clinical characteristics.
Results
If surgery-indicated LI of C-AVS before cosyntropin (pre-LI) were ≥ 3, the right dominant were 109 cases (62 right APA (56.9%) and 2 left APA) and 45 BHA cases (41.3%)), and the left dominant were 52 cases (48 left APA (92.3%) and 4 BHA cases (7.7%)). All of 66 PA cases with pre-LI <3 were diagnosed as BHA by S-AVS. The cases with LI of C-AVS after cosyntropin (post-LI) ≥ 4 were all 104 APA cases, and the cases with post-LI <4 of C-AVS were 144 cases (29 APA cases (20.0%) and 115 BHA cases (80.0%)) diagnosed by S-AVS. ROC analysis of unilateral versus bilateral judged by S-AVS could give us the most suitable pre-LI and post-LI cutoff values of C-AVS for localization diagnosis of aldosteronism.
Conclusions
S-AVS data gave us the more precise localization of hyperaldosteronism as compared to C-AVS data. If we use pre-LI of C-AVS for surgery-indication, we should be very careful about the high prevalence of BHA in right dominant cases. If we use post-LI ≥ 4 of C-AVS, we should also consider the possibility of overlooking at surgery-adaptive APA cases in the cases with post-LI <4.

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GP27

The short synacthen test can be used to predict recovery of hypothalamo-pituitary-adrenal axis function and guide clinical practice

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The 250 mg short synacthen test (SST) is the most commonly used tool to assess the integrity of hypothalamic-pituitary-adrenal (HPA) axis. There are many instances when compromise to HPA-axis function is potentially reversible (including the use of suppressive dose of prescribed glucocorticoids), but currently there are no data to guide clinicians as to the frequency of repeat testing or to the likelihood of HPA-axis recovery. We performed an observational, retrospective, analysis of data from 1912 SSTs from 776 patients (335 men, 441 women, mean age 53 ± 18 years) in whom potentially reversible causes of HPA-axis compromise and adrenal insufficiency(AI) were identified. At least two SSTs were performed in each patient, the median duration of follow-up was 250 days (95%CI, 224-272). Irreversible causes (pituitary radiotherapy, Addison's disease, congenital adrenal hyperplasia, adrenal metastases, bilateral adrenalectomy) were excluded. A separate cohort analysis was performed on patients who had been treated with suppressive dose of glucocorticoids ($n=110$). SST 30-min cortisol level was the best predictor of HPA-axis recovery in patients with reversible AI not exposed to suppressive doses of glucocorticoids (AUC ROC $=0.85$). Patients with 30-minute cortisol levels >350 nmol/l had a significantly shorter time to HPA-axis recovery (341 *vs.* 1580 days, $P=4.4\times10^{-10}$). In this group, 99% of patients recovered HPA-axis within 4-years, contrasting with 34% in those with a 30-min cortisol <350 nmol/l. In the group with a 30-min cortisol <350 nmol/l, a subsequent random cortisol of <200 nmol/l (1-year after the initial SST), identified a population in whom only 11% recovered HPA-axis function. In those patients treated with suppressive dose of glucocorticoids, delta cortisol (30-min – basal) was the best predictor of recovery (AUC ROC $=0.77$). Delta cortisol $>$ 100 nmol/l predicted a shorter estimated median recovery time (262 *vs.* 974 days, $P=7.0\times10^{-6}$). 4-year recovery rates were also different (95% *vs.* 67%). Moreover, no patient with a delta cortisol <100 nmol and a subsequent random cortisol <200 nmol/l recovered HPA-axis function within the 4-year duration of the study. Using a SST 30-min cortisol in patients with reversible causes of AI, and a delta cortisol in those exposed to high doses of glucocorticoids, can predict recovery of HPA-axis function. We believe that these data will help to guide the frequency of repeat dynamic testing and provide a unique dataset that will inform both clinicians and patients as to the likelihood of restoration of intact HPA-axis function.

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GP28

Immunohistochemical staining for histopathological subclassification of primary aldosteronism: nationwide 10-year results from Iceland

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Introduction
Primary aldosteronism (PA) is an important cause of hypertension. Adrenal hyperplasia (AH) and aldosterone-producing adrenocortical adenoma (APA) are considered the most frequent causes of PA. Histopathological analysis of unilateral PA has been difficult since no clear morphological criteria existed for defining aldosterone-producing cells. Recently, the distribution of adrenal cells forming aldosterone and cortisol has been studied by using specific monoclonal antibodies against the enzymes CYP11B2 and CYP11B1, catabolizing the final steps of aldosterone and cortisol production, respectively. In addition to APA and AH, the antibodies allow identification of unilateral multiple micronodules (UMN), expressing CYP11B2 in the zona glomerulosa (ZG), and aldosterone-producing cell clusters (APCC) extending beyond the ZG. The aim of this study was to review the histopathological diagnoses of all patients who underwent adrenalectomy for unilateral PA in Iceland in 2007–2016, using immunohistochemical staining.
Methods
Tissue slides from all patients, aged $\geq$18 years, who underwent adrenalectomy for unilateral PA in Landspitali University Hospital (LUH) in 2007–2016, were accessed and appropriate slides from each patient selected. Antibodies; anti-CYP11B1 (clone 80-7 Mabs 502, rat), and anti-CYP11B2 (clone 41-17B Mabs 1251, mouse), were purchased from Merck Millipore and diluted 1 : 200 using EnVision Flex Antibody Diluent (DM830, Daco). The PA tissue slides were stained along with control samples from healthy adrenal glands using AutostainerLink 48 (Daco). Microscopic evaluation was thereafter performed. All necessary permissions were obtained.
Results
In 2007–2016, a total of 25 patients underwent adrenalectomy as treatment for unilateral PA in LUH. Twenty of them had originally been diagnosed with APA, four with AH and one as inconclusive. After performing the immunohistochemical staining, 7 of the 25 patients' (28%) histopathological diagnoses were changed. In total, 20 of the 25 patients (80%) had APA, three (12%) had APCC and two (8%) had UMN. Out of four patients previously diagnosed with AH, two had APA, one had APCC and one had UMN. One patient previously diagnosed with APA turned out to have APCC and another one UMN. The inconclusive sample proved to contain APCC.
Conclusions
Most of the patients turned out to have APA, with APCC being the second most prevalent histopathological diagnosis. Interestingly, no-one had AH. These findings emphasize the importance of the immunohistochemical staining for the proper histopathological diagnosis of PA patients. Further research is needed regarding APCC and UMN. Moreover, it is important to make further assessment on treatment response in context with precise histopathological diagnosis.

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GP29

Salivary cortisol and cortisone in Cushing diagnosis – reference ranges and clinical cut off limits

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Introduction
Cushing's syndrome is rare, but assessment of patients with clinical suspicion of Cushing's and/or adrenal incidentaloma is frequently required. Thus, there is a need for biochemical screening methods that with high sensitivity and specificity identifies or rule out hypercortisolism. Analysis of late night salivary cortisol allows an easy sampling procedure performed at home and is independent of variations in plasma CBG levels. Analysis by liquid chromatography tandem mass spectrometry (LCMS) allows high analytical specificity and simultaneous analysis of salivary cortisol and cortisone, but robust reference limits and clinical cut-off levels are needed. Analysis of both cortisol and cortisone also allows quality control for contamination by blood or exogenous hydrocortisone.
Objective
Establishing solid reference intervals and clinical cut off levels for salivary cortisol and cortisone in the evening and after low dose dexamethasone suppression (LDDST) test using LCMS.
Methods
Salivary samples were collected at 0800, 2300 and at 0800 h after 1 mg dexamethasone from 175 reference subjects and 24 patients with Cushing syndrome using Salivette® cortisol tubes. Half of the reference group also collected samples at 2000 and 2200. Salivary cortisol and cortisone was analysed with LCMS. Reference interval (2.5th and 97.5th percentile) was calculated non-parametrically and the best cut-off level for discrimination between Cushing patients and reference population was calculated using receiver operating characteristics analysis.
Results
The 97.5th percentile of the cortisol:cortisone ratio was 0.81. Samples with a ratio $\geq$1.0 was excluded from the reference samples for suspicion of contamination of blood or exogenous hydrocortisone. The reference range and cut-off levels for Cushing patients vs. reference population for salivary cortisol and cortisone are presented in the table below. There was no significant difference in salivary cortisol or cortisone at 2200 h compared with 2300 h, whereas the levels were were significantly higher at 2000 h.
Conclusion
A robust reference range for late night salivary cortisol and cortisone and after LDDST for the LCMS method was established. Patients with Cushing's syndrome were separated from the reference population with high sensitivity and specificity and salivary cortisone appeared slightly superior to salivary cortisol. Late night samples may be collected at 2200–2300 h.

Saliva-	2.5th (nmol/l)	97.5th (nmol/l)	Cut-off (nmol/l)	Sensi-tivity (%)	Specificity (%)
cortisol 23.00	0.20	3.61	2.41	100	95.3
cortisone 23.00	1.53	13.50	14.85	100	100
cortisol LDDST	0.02	0.79	0.37	100	85.8
cortisone LDDST	0.59	3.54	4.95	100	100

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GP30

The urinary cortisol metabolome in patients with adrenal insufficiency: dual-release hydrocortisone is less deleterious than conventional hydrocortisone therapy

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Introduction
Oral once-daily dual-release hydrocortisone (DR-HC) therapy provides a more physiological cortisol profile than conventional thrice-daily (TID) replacement therapy and has demonstrated improved metabolic profile among patients with adrenal insufficiency (AI). The mechanisms by which this metabolic improvement occurs may be due to less total exposure, changed cortisol time exposure profile, but also modified metabolism of cortisol.
Objective
The aim was to study steroid enzyme activities related to corticosteroids during DR-HC and TID.
Methods
Patients with primary AI received DR-HC or an equal total daily dose of TID hydrocortisone in a 12-week crossover multi-center study. 24 h urinary collection was performed during both treatment and in 124 healthy controls. Urinary cortisol metabolites were measured using gas chromatography/mass spectrometry providing an index of total cortisol exposure and metabolism.
Results
Fifty patients (22 female, mean age 47 years (range 19–71)) and 124 healthy controls [73 females, mean age 48 years (range 20–81)] were included in the study. Total cortisol metabolites (F, E, THF, 5αTHF, THE, cortols, cortolones) were significantly decreased during DR-HC treatment [median: 6380 µg/24h] compared to TID (8825 µg/24 h); $P<0.001$] and returned to similar value compared to controls (6850 µg/24 h; $P=0.089$). Compared to controls, the urinary THF + 5αTHF/THE ratio reflecting 11βHSD1 activity was increased during both DR-HC ($P<0.001$) and TID treatments ($P<0.001$), being more marked in TID compared to DR-HC ($P<0.05$) compatible with cortisol induced 11βHSD1 activity. Urinary F/E reflecting 11βHSD2 activity was slightly higher in TID versus controls ($P<0.01$), but normalized during DR-HC ($P=0.358$). The 5α-reduced metabolite, 5αTHF, was similar in patients compared to control but decreased significantly with DR-HC compared to TID ($P<0.001$). The 5β-reduced metabolite, THF, was higher in patients compared to control ($P<0.001$) but decreased significantly with DR-HC compared to TID ($P<0.001$). The urinary 5αTHF/THF ratio increased significantly in patients (controls: 1.3; TID: 2.3, $P<0.001$; DR-HC: 2, $P<0.001$) indicating that the main driver for this was an increase in 5β-reductase activity during TID and to a lesser extent during DR-HC.
Conclusion
The urinary cortisol metabolome shows more striking abnormalities in patients receiving TID compared to DR-HC replacement therapy and maybe a more sensitive marker of "optimal cortisol replacement". The increased 11βHSD1 activity in patients on TID may account for the deleterious metabolic phenotype reported in patients with AI and its reduced activity during DR-HC may also mediate some of the beneficial effects previously seen with this treatment.

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GP31

Circular RNA circ0066659 functions as a competitive endogenous RNA by sponging miR-506-3p in adrenocortical carcinoma

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Introduction and objectives
Circular RNAs (circRNAs) represent a class of endogenous noncoding RNAs that have recently been recognized as important regulators of gene expression and pathological networks. However, investigations on adrenocortical carcinoma (ACC) initiation and progression mechanisms only focus on key encoding genes, but neglect shedding an insight into circRNAs.
Materials and methods
We investigated the expression profile of circRNAs in three primary ACC and three Adrenocortical adenoma (ACA) tumor samples using a high-throughput circRNA microarray. Bioinformatic analyses were applied to study these differentially expressed circRNAs. Furthermore, qRT-PCR was performed to confirm these results. The expression levels and functions of circ0066659 were evaluated in ACC clinical specimens and cell lines.
Results
Here we identified 1447 differentially expressed circRNAs in primary ACCs as compared with ACAs, of which 849 were significantly upregulated and 598 were downregulated. Differential circRNAs expression between the two groups were validated by qRT-PCR assay. High expression of cricRNA0066659, one of the upregulated circRNAs in ACC, is closely correlated with a low cumulative survival rate and metastatic progression in ACC patients. Furthermore, our experimental analyses identified that cricRNA0066659 specifically binds to miR-506-3p and has a negative correlation with miR-506-3p, indicating that miR-506-3p as a direct target of cricRNA0066659.
Conclusion
Overall, the differential expression of multiple circRNAs and their clinical significance in ACC tissues as revealed by our study suggests that cricRNA0066659 is a novel metastatic factor and prognostic marker in ACC, we propose that cricRNA0066659 could be used as a potential target in ACC therapy.

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Adrenal Cortex

GP32

***PRKACA* L206R mutation in adrenal Cushing induces histone H1.4 hyper-phosphorylation**

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We previously identified mutations in *PRKACA*, coding for the catalytic a (Ca) subunit of protein kinase A (PKA), as the main genetic alteration in cortisol-producing adrenal adenomas (CPAs) responsible for Cushing's syndrome. Here, we further investigated the mechanism of action of all *PRKACA* mutations identified so far by our team (L206R, L199_C200_insW, S213R_L212_K214insIILR, C200_GlyinsV, W197R, del244-248 + E249Q and E32V). Five out of seven mutants showed reduced binding to at least one of the two tested regulatory subunits (RIa and RIIb). Similarly, not all mutants show increased basal PKA activity. This suggested that the reported mechanism of increased basal activity due to interference with holoenzyme formation was unlikely to be the sole mechanism of action of *PRKACA* mutations. Since most of these mutations lie close to the active site of PKA, we hypothesized that they might alter substrate specificity. Consistent with this hypothesis, a Western blot analysis of PKA phosphorylated substrates using an antibody recognizing the phosphorylated PKA consensus suggested that each *PRKACA* mutation induced specific changes in PKA phosphorylation pattern. These findings were further corroborated by an *in silico* prediction of substrate specificity. Thus, we used a quantitative mass spectrometry method (NanoLC-MS/MS) to precisely analyze and compare the phosphorylation patterns induced by the different mutants. We found that all three tested mutants (L206R, del244-248 + E249Q, C200_G201insV) induced relevant changes in substrate specificity. Among all PKA substrates with increased phosphorylation with the mutants compared to wild-type Ca subunit, histone H1.4 was hyper-phosphorylated at Ser36 by all three mutants. Importantly, we found that CPAs harboring the L206R *PRKACA* mutation ($n=3$) had increased H1.4 phosphorylation at Ser36 compared to non-mutated adenomas ($n=4$). Since H1.4 Ser36 phosphorylation has been shown to be required for mitosis and chromatin condensation, H1.4 hyperphosphorylation might play a relevant part in the mechanisms linking *PRKACA* mutations to increased proliferation of adrenocortical cells. Altogether, these findings indicate that several mechanisms, including a change in substrate specificity, contribute to the development of CPAs caused by *PRKACA* mutations.

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GP33

Alterations in Clock genes expression in human benign adrenal tumors

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Introduction
Alteration in the expression of clock-related genes has been observed in various diseases. Adrenal sensitivity to adrenocorticotropic hormone (ACTH) apart from the hypothalamo-pituitary-adrenal axis is also regulated by the intrinsic adrenal clock. A link between clock genes and glucocorticoid adrenal production has been suggested by *in vitro* and animal studies. In the present study we investigated clock genes expression in human benign tumors of the adrenal cortex. Methods: Sixteen fresh frozen adrenal tissues were collected from November 2016 to December 2017. All patients (13 females/3 males) had adrenalectomy either because of tumor size ($n=7$) or secretory syndrome ($n=9$). *CLOCK*, *BMAL1*, *CRY1* and *PER1* genes expression were analysed with qRT-PCR in benign adrenal tissues (13 adenomas and 3 hyperplasias) and in the peritumoral normal tissue. Protein expression of the aforementioned genes was evaluated by Western Blot analysis. Clinical, biochemical and histological data of the operated patients were also collected retrospectively.
Results
Patients' mean age was 50 ± 13 years old. Four out of 16 patients had overt Cushing syndrome, 2 had subclinical Cushing, 3 had Conn adenomas, and the remaining 7 patients had non functional adenomas (NF). Mean tumor size was 3.7 ± 1.2 cm, Ki-67 was 1–2% and Weiss score 0-1. All clock-related genes exhibited lower expression in adrenal tumors compared to the peritumoral tissue, in the t test paired analysis. However only *CLOCK* and *BMAL1* were significantly down-regulated ($P<0.05$). Moreover, *PER1* showed significant lower expression in NF adenomas compared to cortisol-secreting adenomas, in the Mann-Whitney test (non-parametric analysis).
Conclusion
Our *in vivo* preliminary data demonstrated for the first time that the core clock genes *CLOCK*, *BMAL1*, *CRY1* and *PER1* are differently expressed in adrenal adenomas compared to peritumoral normal tissues, suggesting that dysregulation of the local circadian clock system may play a role in either the development or evolution of adrenal adenomas.

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GP34

Effects of replication of the physiological and non-physiological cortisol rhythm on insulin sensitivity in muscle: a molecular *in vitro* analysis on synchronized muscular cells

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Adrenal insufficiency is a rare endocrine disorder characterized by low levels of cortisol associated with increased mortality, also due to inadequate replacement therapy. The replacement with the thrice-daily immediate release hydrocortisone (IRH), in contrast to the once-daily modified-release hydrocortisone (MRH), more appropriately mimicking the physiological circadian rhythm of cortisol (PCRC), is associated with metabolic disorders, mainly due to the non-physiological peak of cortisol in the evening. The aim of the current *in vitro* study was to compare the effects of exposure to concentrations achieved *in vivo* during the different phases of day after IRH and MRH administration, compared to PCRC, on muscle insulin sensitivity. To this purpose, a mouse skeletal muscle cell line (C2C12), has been used and the *in vitro* oscillation of 24-hour peripheral clock genes expression (BMAL-1, PER-1, PER-2, CRY-2) has been induced by serum shock treatment and analysed by RT-qPCR, allowing to calculate treatment schedules of morning, afternoon and evening exposure (»0800 h, »1300 h and »0600 h), respectively. Simultaneously, the relative expression levels of 84 genes classically involved in muscle insulin sensitivity have been analysed by genomic microarrays and compared between PCRC, IRH and MRH simulated therapies at different times of treatment schedules. In particular, for the evening exposure, microarray analysis showed identical gene expression between IRH treatment and PCRC, whereas MRH caused significant down-regulation of 21 genes relative expression ($P<0.05$) including insulin receptor ($P=0.02$), IRS-1 ($P=0.02$), IRS-2 ($P=0.01$), PI3KCA ($P=0.03$), ADIPOR-2 ($P=0.02$), additionally confirmed by RT-qPCR. Moreover, WB analysis revealed that evening exposure to IRH might reduce intracellular phosphorylated levels of IRS-1 at Tyr608 and of Akt at Ser473 compared to MRH and PCRC treatments suggesting a robust involvement in muscle insulin resistance. In conclusion, these preliminary data demonstrate that, especially for the evening exposure, MRH might preserve the muscle insulin sensitivity otherwise compromised by IRH.

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GP35

The circadian rhythm of glucocorticoid administration entrains clock-controlled genes in blood mononuclear cells: a DREAM trial ancillary study

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Introduction
Adrenal insufficiency requires life-long glucocorticoid replacement. Conventional therapies fail to mimic endogenous cortisol circadian rhythm. Clock genes are essential components of the molecular machinery controlling organ's circadian function and are influenced by glucocorticoids. However, clock genes expression has never been investigated in patients with adrenal insufficiency (AI).
Aim
To evaluate the effect of the timing of glucocorticoid administration on circadian genes expression in peripheral blood mononuclear cells (PBMCs) of AI patients enrolled in the DREAM trial.
Methods
We enrolled 89 AI patients taking conventional glucocorticoid therapy, that were randomly assigned to continue their standard multiple times a day therapy or switch to an equivalent dose of once-daily, modified-release hydrocortisone and 25 healthy matched controls. 83 subjects consented gene expression analysis by realtime qRT-PCR.
Results
Compared to healthy controls, 19 of the 68 genes detected in the PBMC were found differentially expressed in AI patients, at baseline, and 18 restored to control levels 12 week after switching from the standard to once-daily modified-release hydrocortisone, including the core of the clock-machinery: ARNTL[B-MAL] ($P=0.024$), CLOCK ($P=0.016$), PER3 ($P<0.001$) and TIMELESS (<0.001); the Creb-related AANAT ($P=0.021$), CAMK2D ($P<0.001$), CREB1 ($P=0.010$), CREB3 ($P=0.037$), MAPK1 ($P<0.001$), MAT2A ($P=0.013$), PRKAR1A ($P=0.006$), PRKAR2A ($P=0.006$) and PRKCB ($P=0.006$); the transcription factors SP1 ($P<0.001$) and WEE1 ($P<0.001$) and the other circadian-related CSNK1A1 ($P<0.001$), ONP3 ($P<0.001$) and PRF1 ($P<0.001$). Changes in gene expression in PBMCs correlated with metabolic and immune findings.
Conclusions
AI patients on standard multiple times a day replacement therapy exhibit a dysregulation of circadian genes in peripheral blood cells. The switch to the once daily modified-release hydrocortisone reconditions peripheral tissue gene expression to an extent that correlates with the clinical outcomes of the DREAM trial [NCT02277587].

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GP36

Identification of new *ARMC5* missense mutations in Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) and their functional studies *in vitro*

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Introduction
ARMC5 germline and somatic inactivating mutations were discovered in patients treated by adrenalectomy for hypercortisolism due to primary bilateral macronodular adrenal hyperplasia (PBMAH). Since then, several *ARMC5* germline variants have been described in PBMAH patients. Genetic alterations are spread all over *ARMC5* coding sequence and many are missense variants. For them, geneticist conclusions are based on in silico predictions. As for now, no functional assay is routinely performed to study their pathogenic consequences. *ARMC5* is considered as a tumor suppressor gene with proapoptotic function. Our center performs routine germline *ARMC5* sequencing by next generation sequencing for patients all over the country. New missenses have been recently identified. We aimed to develop a functional test to confirm bioinformatics predictions.
Method
In a series of 352 French index cases, 10 new exonic missense variants, not classified as benign polymorphisms by SIFT® and Polyphen2® softwares have

been recently found. For *in vitro* analysis, constructs encoding the potentially pathogenic ones are made in a pIRES vector. Transfections are performed in HEK293 cells to study recombinant ARMC5 protein levels by western blot and cell apoptosis using AnnexinV and propidium iodide staining for flow cytometry (FACS) analysis. Loss of the proapoptotic function of ARMC5 was considered as a marker of mutant pathogenicity.
Results
Seven of these variants were predicted as deleterious or possibly damaging by both SIFT® and Polyphen2®; for the three others, the two softwares predictions were discordant and they were not described in exomes databases. The known variants Leu548Pro, p.Leu331Pro, p.Cys139Arg were previously selected for *in vitro* studies and compared with the predicted benign p.Phe14Tyr variant and wild-type ARMC5. Kinetic analysis were done to study cells apoptosis and ARMC5 protein levels in each condition at three different times between 10 and 16 h of transfection. Preliminary results for these damaging mutants showed decreased markers of apoptosis by FACS assay in comparison with the wild-type and the "benign" variant. Interestingly, the protein levels of the p.Leu548Pro, p.Leu331Pro and p.Cys139Arg "damaging" variants were higher at the longest transfection time than wild-type ARMC5 protein, consistent with more cell death in ARMC5 wild-type expressing cells. Method must be applied to the newly identified missense variants.
Perspective
This approach will help to demonstrate the pathogenicity of the missense variants found in PBMAH patients. This demonstration would be important along with in silico analysis to improve genetic conselling for PBMAH patients and their relatives.

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GP37

MicroRNA expression profiling in adrenal myelolipoma, adrenocortical cancer and adrenocortical adenoma

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Background
Adrenal myelolipoma (AML) is a relatively common and invariably benign tumor composed of adipose tissue and hematopoietic elements. Due to the variable proportion of fat and hematopoietic elements, it is sometimes challenging to differentiate AML from adrenocortical carcinoma (ACC). MicroRNAs have been identified as promising biomarkers in many tumors, including adrenocortical neoplasms, but the microRNA expression of adrenal myelolipoma has not been investigated, yet.
Aims
To perform a large scale microRNA expression profiling in adrenal myelolipoma, benign and malignant adrenocortical tumors to identify potential microRNA biomarkers.
Methods
Next-generation sequencing (NGS) on 30 formalin-fixed paraffin-embedded archived tissue samples (discovery cohort: 10 adrenocortical adenoma (ACA), 10 ACC and 10 myelolipoma) was performed by Illumina MiSeq. Significantly differentially expressed microRNAs were validated by real-time RT-qPCR in an independent validation cohort comprised of 14 ACA, 15 myelolipoma and 12 ACC samples.
Results
We have found relative overexpression of miR- 451a, miR-486-5p, miR-363-3p and miR-150-5p in myelolipoma compared to the other two tumor groups by NGS. For ACC, we have found up-regulation of miR-184, miR-483-5p, miR-431-5p and miR-183-5p compared to myelolipoma and ACA. Validation by RT-qPCR, confirmed significant overexpression of miR-451a, miR-486-5p, miR-363-3p and miR-150-5p in myelolipomas relative to ACA and ACC, whereas significant overexpression of miR-184 was confirmed in ACC relative to the other 2 groups. The overexpression of miR-483-5p has not turned out to be significant in ACC relative to myelolipomas in the validation cohort.
Conclusions
Overexpressed miR-451a, miR-486-5p, mir-363-3p and miR-150-5p might be potential tissue markers of adrenal myelolipoma. The lack of significance in the expression of miR-483-5p between ACC and myelolipoma is remarkable, as miR-483-5p has been considered to be the best marker of adrenal malignancy to date.

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GP38

Identification of a new target of *PRKAR1A* (Carney complex gene): KCTD20 (potassium channel tetramerization domain containing 20) and study of its role in adrenal Cushing

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Introduction
The inactivating mutations of the Carney complex gene *PRKAR1A* (regulatory subunit RIA of PKA) cause bilateral adrenocortical tumors (PPNAD: Primary Pigmented Nodular Adrenocorticel disease) over-secreting cortisol. This leads to stimulation of PKA activity, however the mechanisms of adrenal tumorigenesis and cortisol dysregulation are not fully understood. In order to identify target genes of PRKAR1A inactivation in adrenal cortex we undertook a comparative transcriptome analysis. This work aims to understand the role of the major identified target in cortisol dysregulation and PPNAD development.
Methods
Comparison of the transcriptome of PPNAD tissues, normal human adrenals, and H295R adrenal cortical cells with and without inactivation of *PRKAR1A* identified a main gene whose expression is decreased following *PRKAR1A* inactivation: KCTD20 (potassium channel tetramerization domain containing). The H295R and HEK293 cells were used to understand the transcriptional regulation of KCTD20 by PKA RIA and evaluate the consequences of the inactivation (siKCTD20) and the overexpression of KCTD20 (vector-KCTD20).
Results
The decreased KCTD20 expression after *PRKAR1A* inactivation is independent of PKA activity. Overexpression of KCTD20 increases apoptosis and decreases proliferation. Inactivation of KCTD20 protects against apoptosis ($P<0.01$), increases the activity of the Star-Luc reporter ($P<0.001$), the expression of the Star ($P=0.01$) and CYP11B1 genes ($P=0.05$), and cortisol production of H295R cells ($P<0.05$). These effects seem independent of PKA activity. Invalidation of KCTD20 results in membrane depolarization in response to KCL and increases intracellular calcium ($P<0.001$).
Conclusion
PKA RIA acts on KCTD20 via a PKA independent pathway. KCTD20 may play a role in adrenal Cushing by mechanisms independent of PKA activity. Its role in calcium signalling could be an important element to study.

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GP39

Gene mutation analysis and overal survival among the patints with neuroendocrine tumors of the lung and gastroenteropancreatic neuroendocrine tumors

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Introduction
Neuroendocrine tumors (NET) arise from tissue mucosal cells known as enterochromaffin cells. The clinical behavior of NET has been recognized over the past 30 years and genome analysis are needed for further follow up. Here we conduct integrated genome analyses on data from chromosomal gene copy number and transcriptome sequencing as well as analysis of overal survival of patients diagnosed with NET.
Material and methods
The study accrued 65 patients with NET over a period of 2 years, from 2015 to 2017. During the study period, 36 patients were diagnosed with early and advanced neuroendocrine tumors oft the lung (NETL) and 29 neuroendocrine tumors of the gastroenteropancreatic system (GEP-NET). Tumor-DNA were isolated from fresh-frozen tumour tissue. Whole-genome sequencing was performed using a read length of 2×100 bp. Survival analysis oft the subjects was performed using Kaplan–Meier and Cox regression methods.

Results
Although no significant focal copy number alterations were observed across the tumours analysed, we have detected a copy number pattern compatible with chromothripsis in a sample of carcinoid and pancreatic neuroendocrine tumors. The genomic aterations found in those samples were restricted to chromosomes 3 and 13, and led to the expression of several chimeric transcripts. Wide range of mutations ($n=346$) were identified in chromatin-remodelling genes such as MEN1 and ARID1A. Overal survival was generally good in both groop of subjects, especially in patients with early stage disease (T1-2N0M0: 2-year survival rates of between 88% and 96%). We have not found any relations between gene profile of MEN1 and ARID1A genes and overal survival in both groups of patients.
Conclusion
The overal prognosis of NETL and GEP-NET is much better than the other primary thoracic and abdominal malignancies and is strictly related to tumor classification and TNM stage. We propose a furter gene studies to identify and then confirm genetic predictors of survival in key molecular signaling pathways among patinets with NET. This raises exciting possibilities for treating this disease in the future.

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GP40

Long term imaging follow-up of non-functioning adrenal adenomas at Vilnius University Hospital Santaros Klinikos (VUHSK): 2010–2017

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Background
Currently, the European Society of Endocrinology guidelines asserted against additional imaging during follow-up (FUP) in patients with non-functioning adrenal masses <4 cm in size with clear benign features on imaging studies. Our analysed literature data suggests that an increase (minimum 1 cm) in an initially benign adrenal mass during follow-up occurs in 3.5–20% of patients with adrenal incidentalomas.
Aim
To analyse the change in size of non-functioning adrenal masses detected by computerized tomography (CT) in patients who had FUP at VUHSK from 2010 to 2017.
Materials and methods
A retrospective single-center study of non-functioning adrenal masses was conducted. The following ICD-10 classification codes were used to retrieve cases from our database: D35.0; D44.1; C74.1; C74.9; E26.0; E27,8; E24,8. For the retrospective study of CT scans, electronic data capture system was applied. We considered significant increase as the growth in tumour size by more than 20% and a minimum 5 mm increase in largest diameter.
Results
1250 patients were assessed for adrenal masses from 2010 to 2017. Out of 1250 patients there were 302 subjects (24.16%) with adenomas and at least one FUP and obvious benign features on CT scan were seen, these 302 patients were included in the study. Mean age of study subjects were 65.4 years, 83.2% of them were female. The average tumour size at baseline was 21.5 ± 10.9 mm. Average follow-up (FUP) time was 3.16 years (from 2 to 8) during which tumour size increased in 123 (40,7%), decreased – in 105 (34,8%), did not change - in 74 (24,5%) of cases. Significant increase in tumour size was observed in 22 (7,3%) of cases. Average size of 22 significantly enlarged tumours changed from 19.0 ± 8.5 mm to 33.9 ± 14.9 mm during FUP. Significantly increased tumours were more common in younger age subjects. Subjects age during the tumour discovery: significantly increased 57.3 years (±10.1), insignificantly increased – 61.4 years (±10.5), stayed the same size – 62.6 years (±11.0), $P=0.02955$. None of the observed tumours became functioning during the observation period.
Conclusions
We have demonstrated a significant enlargement of initially benign non-secreting adrenal masses during 3.16 years FUP in 7.3% of cases and the association with younger age. Nevertheless, larger prospective studies with extended FUP are necessary to affirm the time-frame for suitable FUP schemes in order not to miss the significant enlargement of the adrenal mass that necessitate surgical procedures.

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GP41

The need for depression screening in patients with adrenal incidentalomas and (possible) autonomous cortisol secretion – the role of integrated care

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Hypercortisolism is associated with high prevalence of psychiatric disorders and major depression occurs in 50–60% of patients. According to the available literature it is still unknown if patients with (possible) autonomous cortisol secretion ((P)ACS) carry the risk of depressive disorders. The Beck Depression Inventory II (BDI-II) is a commonly used instrument for detecting and quantifying levels of depression and its validity as a screening instrument is well established. The aim of this study was to screen patients with adrenal incidentalomas (AI) – nonfunctional and the ones with (P)ACS, for presence of depression. The study was conducted in Clinic for endocrinology, diabetes and metabolic diseases, Belgrade, Serbia. The total studied group consisted of 72 patients: 40 AI patients (mean age 56.4 ± 7.3 years, mean body mass index (BMI) 28.9 ± 4.6 kg/m^2 and mean adrenal tumor size (ATS) 33.2 ± 9.8 mm) and age matched 32 healthy controls (HC)(mean age 57.6 ± 9.2 years, mean BMI 26.6 ± 4.4 kg/m^2). Based on levels of cortisol after 1 mg-dexamethasone suppression test AI patients were divided in two groups: <50 nmol/l, 17 with nonfunctional AI (NAI) and >50 mmol/l, 23 with ((P)ACS). BDI-II screening tool was used to assess presence of depression. The patients with AI had significantly higher BDI-II score when compared with HC: 19-mild vs. 9-minimal depression, $P=0.002$. In AI group, patients with (P)ACS had significantly higher BDI-II score when compared to NAI: 25-moderate vs. 11-minimal depression. Furthermore, there was a significant positive correlation between the BDI-II score and the levels of midnight cortisol ($\rho=0.527$, $P<0.001$), cortisol after 1mg dexamethasone suppression test ($\rho=0.594$, $P<0.001$) and the ATS ($\rho=0.362$, $P=0.02$). Patients with AI had significantly higher BMI than HC ($P=0.037$). In multivariate regression analysis with levels of midnight cortisol, BMI and ATS, midnight cortisol was the independent predictor of severe depression (OR 1.029, 95%CI OR 1.01–1.05, $P=0.01$). Our study shows that patients with (P)ACS exhibit high prevalence of moderate depressive symptoms. The significant and positive correlation of BDI score with ATS, levels of midnight cortisol and levels of cortisol after 1mg dexamethasone suppression test point to cortisol contribution to the etiology of depression. Our results suggest that patients with (P)ACS should be screened for depression and would benefit from integrated care with psychiatric team.

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Adrenal Medulla and NETs

GP42

Pituitary adenoma and pheochromocytoma/paraganglioma: a multicausal association of tumors

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Background
Pituitary adenomas (PA) and pheochromocytomas/paragangliomas (PCC/PGL) are the main components of MEN1 and MEN2, respectively. Although the presence of both tumors (3P association, 3PAs) in the same patient could be as a result of coincidence, at least in some cases, a common pathogenic mechanism has been involved. Recently has been confirmed that germline mutations in genes coding succinate dehydrogenase (SDH) play a role in pituitary tumorigenesis. Furthermore, MEN1 germline mutations have also been identified in patients with 3PAs.

Aim
To report the clinical data, management outcome and genetic mutations found in a multicenter retrospective study of 10 patients with 3PAs.
Results
Six patients were female and 4 male. Mean age at diagnosis of the first tumor was 51.6 years (range 36–73). PA was firstly detected in 6 patients and PCC/PGL in 4 cases. Acromegaly was present in 6 cases (3 microadenomas). The remaining PA were prolactinoma (3 patients) and non-functioning PA (NFPA) in 1 patient. Regarding PCC/PGL, 7 patients had a single tumor (4 PCC and 3 PGL) and in 3 cases multiple or bilateral disease was diagnosed (2 PGL and 1 PCC). Patients with acromegaly and the patient with NFPA underwent surgery. Patients with prolactinomas received medical treatment with dopamine agonist and one case required surgery because of drug intolerance. Unilateral adrenalectomy was undergone in all single 4 PCC and a bilateral procedure was performed in the patient with a bilateral tumor. Single tumor was resected in two cases with PGL. In one of the patients with multiple PGL, the largest cervical mass was removed and in other patient the mediastinal tumor was unresectable because of close proximity to vascular structures. In all cases, genetic tests were implemented. In 4/10 patients genetic investigation was positive. We found SHDB (1p36) mutation in one patient, SDHB exon 1 delection in one patient, SDHD (P81L exon 3) mutation in one patient and 1 MEN1 mutation in a further patient. In the remaining 6 patients genetic tests performed were negative.
Conclusion
The 3PAs is a very uncommon event and recent data provides strong evidence that PA can develop in patients with germline SDH mutations. MEN1 germline mutations have also been related to these patients. Genetic testing should be considered in all patients with this tumor association.

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GP43

Ex vivo metabolomic profiling in phaeochromocytoma, paraganglioma and GIST tumours: lessons learned

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Recent discoveries in mutations in TCA cycle enzymes; succinate dehydrogenase (SDH), fumarate hydratase (FH), iso-citrate dehydrogenase (IDH) and malate dehydrogenase MDH2, have reinforced the link between mitochondrial dysfunction and cancer[1]. Phaeochromocytoma and paraganglioma (PPGL) are now recognised to be the most heritable tumour, with 40%[1] having a genetic defect. Mutations in the *SDH* genes are the most frequently implicated genetic abnormality in hereditary PPGL and are also implicated in the development of wild type GIST tumours. The aim of this study was to evaluate the translational utility of *ex vivo* metabolomics profiling of PPGL and GIST tumours by HRMAS ^{1}H NMR spectroscopy. HRMAS ^{1}H NMR data acquisition was performed on 30 fresh frozen tumour samples (26 PPGL and 4 GIST). Absolute metabolite concentrations were estimated by fitting the metabolite signals in the water-suppressed HRMAS ^{1}H NMR spectrum in LCModel and using tissue water signal as internal standard for absolute concentration[2]. The lactate, glutamate and glycero-phosphocholine (GPC) concentrations were significantly lowered in *SDH* mutated tumours compared to wild type (WT) tumour tissues, whereas succinate was several folds higher in *SDH* mutated tumours tissues. A cut off of greater than 0.61 mmol/l was established to distinguish between *SDH* mutated tumours and wild type or other hereditary causes of PPGL, with a sensitivity of 95% and specificity of 100% on ROC curve analysis. Significantly lower lactate indicates down regulation of glycolysis in *SDH* mutated tumours compared to WT tumours. Lowered glutamate, aspartate and choline containing compounds (GPC and t-Choline) indicates reduced amino-acid and membrane phospholipid metabolism in *SDH* mutated tumours. These key differences in the metabolomic fingerprint of *SDH* mutated tumours suggests specific metabolic vulnerability and requires further investigation to determine if this vulnerability can be exposed for therapeutic intervention. One paraganglioma sample was detected to have 2 hydroxyglutarate (2HG) accumulation and subsequent genetic sequencing identified a somatic *IDH1 (R132C)* mutation in the PGL. Detection of succinate accumulation in a single wild type GIST tumour was relevant in determining the pathogenicity of a novel *SDHA* variant, identified in the germline of that patient.
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GP44

Mortality in patients with Pheochromocytoma: a population-based study 1977–2016

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Background
Pheochromocytomas and catecholamine-secreting paragangliomas (PPGL) are rare catecholamine-producing tumors. Due to the rarity, limited data on prognosis exists and data are mainly from tertiary centers with potential referral bias. Here, we present population-based mortality data over an observation period of 40 years.
Materials and methods
We identified a cohort of 198 PPGL patients diagnosed 1 January 1977 to 31 December 2016 in North and Central Denmark (population 1.75 million). Data on tumor size, tumor location, surgery and recurrence were obtained from health records. Date of death or emigration was obtained from the Civil Registration System. Hazard rate-ratios (HRR) for death or tumor recurrence were calculated using Cox regression and adjusted for sex and age at diagnosis.
Results
Radically operated ($n=162$, 81.8%) patients (median age 52.0 years (Q1–Q3: 39.3–63.0)) had an overall 5- and 10-year survival after surgery of 90.8% (CI95%: 84.5–94.6) and 78.7% (CI95%: 69.8–85.2) and a recurrence-free 5- and 10-year survival of 87.0% (CI95%: 80.1–91.7) and 75.7% (CI95%: 66.7–82.7), respectively. HRR for death or recurrence was not associated with tumor size or with extra-adrenal location of tumor. Twelve (6.1%) PPGL patients did not undergo radical surgery as they either died before surgery ($n=2$), had disseminated disease ($n=4$), abstained from surgery ($n=4$) or since radical surgery was not technically possible ($n=2$). For these patients, median time from diagnosis to death was 5.3 years (Q1–Q3: 0.3–16.4). Twenty-four (12.1%) PPGL patients were diagnosed at autopsy. Based on autopsy reports, PPGL was regarded the underlying cause of death in 5 (20.8%) patients, a contributing cause in 14 (58.3%) patients and an incidental finding in 5 (20.8%) patients.
Conclusion
PPGL patients who undergo radical surgery have a good long-term prognosis with three-fourths of patients living more than ten years after surgery. Those who are not radically operated are a heterogeneous patient group with a relatively short life expectancy. This, combined with the fact that PPGL was considered a direct or contributing cause of death in many patients diagnosed at autopsy, underlines the importance of early diagnosis and treatment of PPGL.

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GP45

The 10 Hounsfield Units cut-off value on unenhanced CT imaging is highly sensitive to diagnose pheochromocytoma: a multicenter study

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Introduction
A substantial proportion of pheochromocytomas (PCC) are detected during the work-up of an adrenal incidentaloma. Recently it has been suggested that in case of an adrenal incidentaloma with an unenhanced attenuation value <10 Hounsfield Units (HU) on CT imaging biochemical testing to rule out PCC is unnecessary. We aimed to determine the sensitivity of the 10 HU cut-off value to detect pheochromocytoma.
Methods
Retrospective multicenter study with reassessment of preoperative unenhanced CT-scans performed in patients in whom a histopathologically proven PCC had been diagnosed from 2000 until 2017. Tumor characteristics including unenhanced attenuation values, were determined independently by two experienced radiologists. Sensitivity of the 10 HU threshold was calculated and interobserver consistency was assessed using the intraclass correlation coefficient (ICC). Data are provided as mean $+/-$SD or median with IQR, where appropriate.
Results
For this analysis 214 patients were identified harboring a total number of 222 PCC. Maximum tumor diameter was 51 [39–74] millimeter. The mean attenuation value in the transversal plane was 36 ± 10 HU. There was only one pheochromocytoma with an attenuation value <10 HU resulting in a sensitivity of 99.6% (95% CI: 97.5–99.9). ICC was 0.81 (95% CI: 0.75–0.86) with a standard error of measurement of 7.3 HU between radiologists.
Conclusion
The likelihood to encounter a PCC with an unenhanced attenuation value <10 HU on CT imaging is very low. This supports the recommendation to only perform biochemical testing to rule out pheochromocytoma in patients with an adrenal incidentaloma demonstrating unenhanced attenuation values >10 HU. The interobserver consistency in attenuation measurement is excellent.

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GP46

Comparative study between incidental and symptomatic pheochromocytoma

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Introduction
The widespread use of abdominal computed tomography and magnetic resonance imaging has led to a rise in the diagnosis of incidental adrenal lesions, some of them are pheochromocytomas (Pheo).
Objective
To investigate the differences between incidental (IPheo) and symptomatic Pheo (SPheo).
Methods
A multicenter retrospective study on clinical and pathological characteristics, treatment and outcome in patients with Pheo followed up in neuroendocrinology units who underwent surgery between 1981 and 2016 was performed. The diagnosis of IPHeo was established when the adrenal lesion was discovered on a previous imaging study performed for an unrelated reason.
Results
Seventy-two patients with Pheo [44 SPheo (61%) and 28 IPheo (39%)] were studied. Age at diagnosis was significantly higher in IPheo than in SPheo patients [mean age 57 ± 13 year vs 49 ± 14 year; $P=0.018$]. There were no significant differences in sex distribution.The tumor was sporadic in 86% ($n=24$) of IPheo and in 80% ($n=35$) of SPheo (NS). The prevalence of hypertension at diagnosis was similar in both groups of patients [10 (35.7%) IPheo and in 18 (40.9%) SPheo, NS]. The 24-hour urinary fractionated metanephrines were less frequently elevated in IPheo than in SPheo patients (31% vs 70%, $P=0.024$). The elevation of 24-hour urinary catecholamines excretion was similar in both groups (78% vs 70%, NS). One patient (3.6%) had normal urinary catecholamines and metanephrines in IPheo group vs 3 (7.6%) in SPheo (NS). Complications during surgery were similar in both groups (15% in IPheo vs 29% in SPheo, NS). The tumor size was significantly lower in IPheo than in SPheo [4.9 ± 2.3 cm (range, 1.5–10) vs 6.4 ± 2.9 cm (range, 2.4–13), $P=0.037$]. There were no differences in both capsular and vascular invasion [5 (19%) IPHeo vs 7 (18%) SPheo, NS], as well as in the presence of necrosis [6 (24%) IPHeo vs 7 (19%) SPheo, NS], and recurrence rate between both groups. No patient had metastasic or persistant disease in IPheo group while 3 patients (6.8%) showed it in SPheo. One patient (3.6%) had recurrent disease in IPheo group vs 6 (13.6%) in SPheo (NS).
Conclusion
In our series IPheo affect older people and are smaller than SPheo. Urinary metanephrine are less frequently elevated in IPheo than in SPheo. Any incidental adrenal mass should be investigated for possible pheochromocytoma despite the absence of symptoms. Lastly, a normal hormonal study does not completely rule out the presence of a Pheo.

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GP47

Identifying active steroids, steroid receptors and pathways in the normal breast and their potential relationship to obesity and cancer development

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Introduction
While a great degree of focus has recently been placed on identifying novel steroidogenic pathways that are active in cancer development (e.g. Androgen metabolism and Androgen Receptor (AR) Signalling, Glucocorticoid Metabolism and Glucocorticoid receptor (GR) signalling) very few studies have examined these pathways in normal breast samples taken under non-pathological conditions. Furthermore, very few studies have examined the steroid levels in non-pathological breast samples.
Methodology
To address this we examined the immunoreactivity of AR, GR and their related enzymes in forty paraffin embedded-formalin fixed samples taken from mammary reduction surgery. In parallel, we examined the levels of steroids via GC–MS/MS in distal to tumour, histological normal samples, taken during surgery for breast cancer in order to identify the steroids present in these samples and any changes between these and tumour levels of steroids.
Results
AR, 5αR1 and 17βHSD5 as well as GR, 11βHSD1 and 11βHSD2 were apparent in the lobules and ducts of normal breast tissues. In an initial analysis of a subset of the samples, both receptors were associated with their cognate enzymes, although these associations did not reach statistical significance. Most interestingly, GR expression was correlated with that of androgen-altering enzymes (<0.01, 5αR1 $R^2=0.33$ and 17βHSD5 $R^2=0.56$). As BMI is considered a potential risk factor in the development of breast cancer, we tested the correlation between BMI and the level of expression of GR and AR. This analysis showed that a higher BMI correlated with higher expression of AR ($P=0.04$, $R^2=0.23$). When analysing the levels of steroids present in histological normal, distal to cancer tissues we found that the most abundant sex steroid was DHEA with the following hierarchy of steroids DHEA$>$Adione$>$T$>$E2$>$DHT, and the two steroids that varied significantly between matched normal and cancer samples were E2 (increased in cancer) and Adione (decreased in cancer) suggesting the importance of localised metabolism of steroids.
Conclusions
Our data suggests the importance of intracrine conversion of steroids in the normal breast and the presence of complete (ligand, enzyme and receptor) significant intracrine pathways. It also suggests some linkage between obesity, a potential risk factor in breast cancer development, and expression of GR and AR in breast cancer tissues.

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GP48

In vitro studies reveal a potential therapeutic role of the combination of biguanides and statins for the treatment of prostate cancer

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Prostate cancer (PCa) is the most common tumor pathology in men worldwide. The medical treatments currently used as first-line therapy after surgery are anti-androgens like abiraterone or enzalutamide, which, unfortunately, fail to stop the disease in a high percentage of cases, resulting in progression towards aggressive castration-resistant PCa. Therefore, new therapeutic tools to manage PCa are urgently needed. Biguanides and statins, two types of drugs commonly used in metabolism-related pathologies (i.e. type 2 diabetes, hypercholesterolemia and obesity) have been recently shown to exert antitumoral actions in several cancers. Here, we aimed to determine the antitumoral capacity of biguanides, statins and their combination in human PCa cells. To that end, different biguanides [metformin (5 mM), buformin and phenformin (1 mM)], statins [atorvastatin, simvastatin and lovastatin (10 μM)] and selected combinations were tested in PCa-derived cell-lines (22RV1, LNCaP, PC3 and DU145), in the normal prostate cell-line (RWPE-1), and in normal primary prostate cell-cultures obtained from healthy donors, by using different functional assays (i.e. cell proliferation, migration, tumorosphere formation, clonogenic assay, etc). Results revealed that all biguanides and statins reduced cell proliferation at 48- and 72-h in all the PCa cell lines tested (except statins in DU145 cells), being the effect of phenformin and simvastatin significantly higher compared with metformin/buformin and atorvastatin/lovastatin, respectively, in most of the PCa cell-lines. Interestingly, the combination of metformin with atorvastatin or simvastatin exerted a synergistic inhibitory effect on cell proliferation. Of note, the inhibitory effect caused by biguanides, statins or their combination in cell proliferation was significantly less pronounced in normal prostate cells (RWPE-1 and primary cell cultures) compared to that observed in PCa cell lines. In addition, metformin, simvastatin and its combination significantly reduced cell migration in all PCa cell-lines, being this effect additive when both compounds were co-administrated in LNCaP and DU145 cell-lines. Furthermore, the strong antitumoral effect of biguanides and statins observed in PCa cells was reinforced with the results showing that combined treatment with both compounds inhibited tumorosphere and colony formation. Altogether, our results revealed that biguanides and statins are able to reduce tumor aggressiveness *in vitro*, being this effect significantly higher when these compounds are combined, suggesting a potential therapeutic role of these compounds, especially their combination, for the treatment of PCa.

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GP49

Targeted destruction of FSHR-positive cancer cells by a lytic Phor21-FSHb conjugate

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Expression of the follicle-stimulating hormone receptor (FSHR) has been shown in gonads, gonadal tumors, and in endothelial tumor vessel cells of various cancers. We investigated the specificity and cytotoxicity of a fusion lytic peptide Phor21, conjugated to different FSHβ-chain fragments to ablate FSHR expressing cancer cells *in vitro* and *in vivo*. Cytotoxicity of 12 different Phor21-FSHβ conjugates was tested in HEK-293 cells, stably transfected with human FSHR cDNA (HEK293-FSHR) or mock-transfected HEK-293 cells used as FSHR-negative control cells. Phor21 linked to FSHβ33-53 fragment with cysteine (Cys) replaced by serine (Ser) (Phor21-FSHβ33-53C/S) displayed dose-dependently the highest specific cytotoxicity towards HEK293-FSHR cells vs. other compounds. Competitive studies with recombinant human FSH (rhFSH, 100 IU/l) significantly decreased the cytotoxicity of Phor21-FSHβ33-53C/S conjugate in HEK293-FSHR cells. *In vivo* Phor21-FSHβ33-53C/S treatment significantly inhibited the growth of HEK293-FSHR xenografts inducing necrosis. The efficacy of Phor21-FSHβ33-53C/S was enhanced by the GnRH antagonist cetrorelix (CTX) co-treatment. CTX alone displayed pro-apoptotic action. The growth of LNCaP cell xenografts, with previously reported FSHR-positive tumor vessel endothelial cells, was significantly inhibited by CTX, whereas Phor21-FSHβ33-53C/S showed no effect. We, therefore, revisited the expression of *Fshr* in LNCaP xenograft murine vessels. No *Fshr* transcripts in the endothelium of tumor vessel cells could be found. Our results emphasize the strong need to clarify the functional FSHR expression in the tumor vessel endothelial cells and different cancer cell lines. We proved the principle that the Phor21-FSHβ33-53C/S conjugate may provide a novel specific therapeutic lead into the targeted destruction of FSHR expressing cancer cells.

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GP50

Abstract withdrawn.

GP51

Evolution of mesenteric metastasis in small intestinal neuroendocrine tumours (SI-NETs)

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Background
A metastatic mesenteric mass is a hallmark of small intestinal neuroendocrine tumours (SI-NETs). However, little is known about the evolution of a SI-NET-associated mesenteric mass over time.
Methods
Retrospectively, 530 patients with proven SI-NET and $\geq$2 available CT-scans were assessed for clinical characteristics at diagnosis and the presence and growth of a mesenteric mass on every consecutive CT-scan until end of follow-up or resection and in correlation with receiving Peptide Receptor Radionuclide Therapy (PRRT).
Results
A mesenteric mass was present in 64.2% of the patients of whom 13.5% showed growth of mesenteric mass according to RECIST 1.1. In patients without a mesenteric mass, only 2.6% showed growth of preexisting small nodule or development of new mesenteric mass. The median time to growth was 37.1 months. Independent predictors of growth were having a mesenteric mass (OR 8.14, 95% CI: 2.41–27.44, $P=0.001$) and male gender (OR 1.97, 95% CI: 1.03 – 3.75, $P=0.04$). Furthermore, of the patients treated with PRRT ($n=132$), only 4.4% had a reduction of their mesenteric mass according to RECIST 1.1.
Conclusion
Absence of a mesenteric mass at diagnosis of a SI-NET is associated with a low chance on development of a mesenteric mass over time. If present, we found that the hallmark dominant mesenteric mass in SI-NETs shows a highly inert behavior when assessed by RECIST 1.1 criteria and the only independent predictors of growth were having a mesenteric mass and male gender. Additional studies are needed to explore a possible role of sex steroids in the pathogenesis of SI-NET-associated mesenteric mass. Finally, shrinkage of the mesenteric mass after PRRT occurred in a small subset of patients, indicating a differential response to PRRT compared to other NET localizations.

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GP52

Epidemiology and clinical significance of clinical hormonal syndromes in patients with neuroendocrine tumors

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Introduction
Hormonal syndromes are significant cause of morbidity in patients with neuroendocrine tumors (NET), requiring special treatment, rarely completely efficient. Effect on mortality is also presumed. Our aim was to investigate epidemiological characteristics of NET with hormonal production in our group of patients.
Patients and methods
We analyzed 822 patients with NET of various primary tumor sites, treated at our department during period of 2004–2017. Tumors were graded and staged according to pathohistological characteristics, and extent of dissemination. Hormonal analyses were done routinely according to clinical presentation. Immunohistochemical staining for specific hormonal products was performed in tumors with proven clinical syndrome, and in gastro-entero-pancreatic (GEP) NET irrespective of presence of clinical syndrome. Statistical analysis was done with SPSS software.
Results
A total of 155 patients (18.9%) had hormonal clinical syndrome in our group of patients with NET. Immunohistochemical positivity without clinical syndrome was verified in additional 63 patients with GEP NET, making it a total of 218 (26.5%) tumors producing some type of hormonal product. Serotonin production was most frequently detected (126 tumors, 15.3%), followed by insulin in 21 tumors (2.6%), gastrin in 20 tumors (2.4%), ACTH in 15 tumors (1.8%), somatostatin in 10 tumors (1.2%), and calcitonin in 8 tumors (1.0%). Less frequently, ghrelin, glucagon, GHRH, VIP, PTHrP and ADH production was detected (in less than 1.0% each). In 39 patients without carcinoid syndrome, serotonin immunopositivity was detected in tumor tissue. Conversely, 6 patients with clinical carcinoid syndrome stained negative for serotonin. Same was observed in about 50% of patients with clinical ectopic Cushing's syndrome. Only one patient immuno-positive for somatostatin actually presented with clinical syndrome. Hormonal clinical syndrome was most frequently present in patients with intestinal NET (47 patients, 30.3%), followed by pancreatic (46 patients, 29.7%), and lung NET (26 patients, 16.8%). Significant proportion consisted of tumors of unknown primary site (30 patients, 19.4%). Clinical syndrome was rarely present in poorly differentiated NET, only in 11 patients with grade 3 tumors. Overall survival in patients with hormonal syndromes was 126.0 months (95%CI 61.6–190.4), with 5-year survival of 62.5%. This was not significantly different when compared to non-functioning grade 1 and grade 2 NET ($P=0.929$). Only presence of Cushing's syndrome significantly affected survival (median 4.0 monhs, 95%CI 0.0–12.1)
Conclusion
Clinical hormonal syndrome in patients with NET has a significant impact on overall morbidity, but seems not to affect survival, except in case of ectopic Cushing's syndrome.

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Bone and Osteoporosis

GP53

Online bots could help in prevention and treatment of osteoporosis

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Introduction
It is too much easier and cheaper to prevent a decrease a bone density and fractures, than in the future to treat osteoporosis and its complications.
Materials and methods
We used an online system for patient education based on the video lessons to convey the necessary information on good nutrition, necessary to do exercises and the need for exposure to the sun. Also we added individual online doctors management.
Study results
Watching the short movies, the patients formed the habits of good nutrition during the first month already, which includes a diet with restriction of fat, digestible carbohydrates and daily consumption of low-fat dairy products, slow carbohydrates, protein and fiber. Were also presented recommendations for compliance with the physical activity, as well as vitamin D and calcium consumption. Also we added individual online doctors management, which include everyday motivation and chatting with doctors 24 hours a day. We examined data from a survey of 520 patients registered in the online system www.rightdiet.ru and 50 patients control group who were given the same recommendations on the appointment and 67 patients with online management. Surprisingly, the consumption of milk and dairy products increased by 2.6 times, compared with patients in the control group and 3.4 in management group. The exposure to the sun was observed 15–30 min daily, compared with the control group 5 min. Regular physical activity were the main group of 260 min per week, in control group 80 min and 380 min in management group.
Conclusions
Very important how we can make delivery of the material. We live in a World of high technologies and lack of time. Often the patient has no opportunity to go to the doctor for an appointment, and during reception it is not always possible to discuss all aspects, and even if it was possible, some information is forgotten by patients. Everyday management group has better results because of increasing motivation and reminders. So, we would like to use online bots for everyday motivation and answer a simply questions to improve the quality and duration of life of more our patients.

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GP54

Effect of inhaled corticosteroidson trabecular bone score in patients with asthma

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Background
In asthmatic patients, in addition to conventional risk factors for osteoporosis, inflammatory factors and treatment with corticosteroids may also lead them to further bone loss. The trabecular bone score (TBS) is a new indirect parameter of bone quality. There has been no study which evaluates TBS in asthmatic patients according to use of corticosteroids.
Objective
This study evaluated the TBS according to the severity of asthma and the correlation of TBS with steroid dose and the severity of asthma in patients with asthma.
Methods
This study had a cross-sectional design. Six hundred twenty-seven patients with asthma and the same number of non-asthmatic controls matched for gender and age were included in this study. The TBS was calculated in the lumbar region, based on two dimensional (2D) projections of dual-energy X-ray absorptiometry (DXA) assessments.
Results
Patients with severe active asthma exhibited a lower vertebral TBS than those with non-severe asthma, non-active asthma, and non-asthmatic subjects, whereas there were no significant differences in bone mineral density (BMD) among the study groups. TBS was significantly associated with the cumulative systemic steroid dose and high inhaled corticosteroids (ICSs) exposure over 3000 mg during previous 1 year, even after adjusting for confounding factors. TBS was also significantly correlated with FEV1/FVC and methacholine PC 20 suggesting that airway inflammation.
Conclusion
Severe active asthma patients exhibited a lower vertebral TBS regardless of age groups. TBS was significantly associated with the cumulative systemic steroid dose and high ICS exposure over 3000 mg of fluticasone equivalent dose, which was not correlated with BMD. TBS can be used for an early detector of the alterations in bone quality which are a consequence of glucocorticoid therapy or possibly the exacerbation of asthma.

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GP55

Association between diabetes and the risk of falls: a nationwide population-based study

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Background
This study examined the associations between diabetes (DM) and falls in Korean using data from a large population-based survey.
Methods
This study analyzed 126 200 men and women (aged ≥50 years) who participated in Korean Community Health Survey in 2013. Logistic regression was used to assess the relationship between DM and falls.
Results
The mean (±S.D.) of age, and body mass index was 64.9±10.0 years and 23.2±2.9 kg/m^2. We identified 18,916 individuals with DM (91.6% with oral antidiabetics or no medication [DM-O], and 8.4% with insulin [DM-I]) and 107,284 individuals without DM. A total of 20 419 (19.0%) non-DM subjects, 3921 (22.6%) DM-O patients and 485 (30.6%) DM-I patients had histories of falls. After adjustment for potential confounders, the odd ratio (OR) for falls in DM-O group and DM-I group were 1.09 (95% CI: 1.03-1.16) and 1.76 (95% CI: 1.52–2.04) compared with non-DM group. Corresponding results for recurrent falls (≥2 times per year) in DM-O group and DM-I group were 1.15 (95% CI: 1.05–1.25) and 2.15 (95% CI: 1.77–2.62).
Conclusions
The risk of falls was increased in diabetes patients, particularly among those using insulin.

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GP56

The influence of adipose tissue and bone marrow fat on bone mineral density in short bowel syndrome

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Short bowel syndrome (SBS) is a complex disease, occurring after extensive resection of the small intestine, leading to malabsorption of nutrients and fluids. Lipids storage significantly affects bone maintenance. Caloric restriction promotes bone and adipose tissue (AT) loss but marrow adipose tissue (MAT) expansion. SBS is a condition strongly associated with malnutrition; patient survival initially depends of caloric replacement through parenteral nutrition (PN). The present study was designed to prospectively evaluate the association of subcutaneous (SAT), visceral (VAT), intra-hepatic lipids (IHLs) and MAT on bone mineral density (BMD) in SBS patients. Also, it was investigated the relationship between adipose tissue and bone markers [osteocalcin (OC) and C-terminal telopeptide of type I collagen (CTX)]. The study comprised two groups matched by age, sex and height: a) control group (CG) (n=18; 9M, 9F) and b) SBS group that was evaluated two times, (SBS0; n=14; 7M,7F) at 6.5 years after enterectomy and 1 year latter (SBS1; n=11; 6M, 5F). Magnetic resonance was used to measure AT (^{1}H spectroscopy for MAT). SBS group showed a non-significant decrease in BMD throughout the study, but BMD was lower in SBSG0 and SBS1 than in CG. IHLs were higher in SBS0 and SBS1 than in CG. CTX was lower in SIC0 comparing to CG (CG=0.36±0.19×SIC0=0.81±0.57). Values of MAT, SAT, VAT and OC were similar between groups throughout the study. MAT was negatively correlated with L3 BMD in the CG (r=-0.6; P<0.05), but not in the SBS group (SBS0 r=0.45; P=0.13; and SBS1 r=0.45; P=0.17). After adjustments by body mass index (BMI) and age, the association disappeared (R^2=0.09; P=0.91). IHL was negatively and significantly associated with femoral neck BMD (R^2=0.16; P<0.05) and total hip BMD (R^2=0.27; P<0.05). Moreover, IHL was positively and significantly associated with CTX (R^2=0.46; P<0.05). There was no association between MAT and CTX. Osteoporosis is a frequent complication in SBS patients. MAT amount is not increased and there is no negative relationship between MAT and BMD in SBS. Access to calories seems to positively affect the relationship between MAT and bone mass in malnutrition. The accumulation of IHLs negatively affects bone mass in SBS patients.

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GP57

Kinesiotherapy rehabilitation program to correct deep core stability muscle dysfunction in patients with osteoporotic vertebral fractures

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Objective
The study is aimed to estimate the effectiveness of kinesiotherapy based on deep core stability muscles training in the program of rehabilitation in patients with osteoporotic vertebral fractures (VF).
Material and methods
Fourty-five patients (M-4, F-41) aged 43-81 (average age 62.75±12.5) with primary osteoporosis and at least one non-traumatic VF were included in the study. The rehabilitation program focused on training of deep core stability back muscles and consisted of 4 kinesiotherapy methods (Dr Wolff and CBS simulators, kinesiohydrotherapy in the pool and complex physical exercises by Gorinevskaya-Dreving) was prescribed for 21 days to all patients. Isometric core strength test (Back-Check, Dr Wolff, Germany) was performed at baseline, at the end of the rehabilitation treatment and after 21 day past all training at follow-up visit.
Results
At baseline relative flexion strength (REL FS), relative extension strength (REL ES), left lateral flexion strength (LLAT FS), right lateral flexion strength (RLAT FS) were lower than recommended indexes: 113.01±34.03% of 150% (P=0.001), 75±12.78% of 100% (P=0.006), 85±12.78% (P=0.04) and 79.73±9.2% of 100% (P=0.003) accordingly. Ratio relative flexion/extension strength (FLE:EXT S) also was in imbalance in 38 of 45 patients. Lateral flexion ratio (LLAT:RLAT FS) showed imbalance only in 6 patients. The all isometric core strength test indexes improved significantly: REL FS up to 132.57±47.08% (P=0.0001), REL ES up to 86.45±9.4% (P=0.03), LLAT FS up to 90.7±9.55% (P=0.07), RLAT FS up to 89.4±2.5% (p=0.03) after the rehabilitation course. The muscle strengths stay better than the baseline indexes at the follow-up measurement: REL FS =121.5±39.9% (P=0.002), REL ES =79.78±10.5% (P=0.02), LLAT FS =87.1±11.07% (P=0.06), RLAT FS =80.14±8.62% (P=0.09).
Conclusions
The basic dysfunction of deep core muscles and disbalance flexion/extension strength in osteoporotic patients with VF were estimated. Rehabilitation program using kinesiotherapy in patients with VF showed the high prolong effect on improving back muscle strength.

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GP58

Investigating glucocorticoids as mediators of increased bone marrow adiposity during caloric restriction

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Background
Bone marrow adipose tissue (BMAT) comprises >10% of total adipose mass in healthy humans and further increases in diverse clinical conditions, including obesity/diabetes, osteoporosis and following caloric restriction (CR). However, why BMAT increases during CR remains unknown. One possibility is that this is mediated by glucocorticoid (GC) excess**.** GC action on target tissues depends on circulating and intracellular concentrations of the active hormone (cortisol in humans; corticosterone in rats/mice). Most effects of endogenous glucocorticoid excess are mediated by 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1), which catalyses intracellular regeneration of active glucocorticoids from inert 11-keto forms. CR increases circulating GCs, and GC therapy increases BMAT; thus, *we hypothesise that GC excess mediates BMAT expansion during CR.*
Objectives
Determine 1) if bone marrow expresses 11b-HSD1; 2) if CR increases GC activity within bones; and 3) if ablation of 11b-HSD1 blocks CR-induced BMAT expansion.

Methods
1) *HSD11B1* mRNA was measured in bone marrow from hip-replacement patients. 2&3) Male and female C57BL/6J mice lacking *11b-HSD1* ($Hsd11b1^{Del1/Del1}$) or littermate controls (WT) were fed *ad libitum* (AL) or 70% of AL intake (CR) from 9 to 15 weeks of age and skeletal GC target gene expression determined. Body mass, composition, and plasma were measured weekly. At 15 weeks mice were euthanised. Plasma corticosterone and 11-dehydrocorticosterone were measured by ELISA or LC–MS/MS. Bone loss (calcified bones) and BMAT (*decalcified, osmium-tetroxide-stained bones*) were measured by micro-computed tomography.
Results
1&2) 11b-HSD1 was expressed in bones and marrow of mice and humans. CR in mice increased expression of GC target genes in bone, suggesting increased GC action. 3) In WT and $Hsd11b1^{Del1/Del1}$ mice, CR decreased body and lean mass and increased circulating corticosterone. Consistent with previous studies, in both genotypes CR decreased fat mass only in male mice. Circulating 11-dehydrocorticosterone was significantly greater in AL and CR $Hsd11b1^{Del1/Del1}$ mice than WT controls. While CR-induced bone loss was negligible, CR-induced BMAT expansion occurred in females of both genotypes and in WT males, but not $Hsd11b1^{Del1/Del1}$ male mice.
Conclusions
CR increases GC action within bones; BMAT expansion is not sufficient for bone loss; and intracellular GC activation by 11b-HSD1 is required for CR-induced BMAT expansion in male, but not female mice. These findings highlight glucocorticoids as potential mediators of BMAT formation and identify novel sex-dependent differences in the skeletal and metabolic adaptations to caloric restriction.

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GP59

Thirty-one men and women with145 spontaneous vertebral fractures after denosumab discontinuation: a single center observational study

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Denosumab discontinuation (DD) induces an increase of B-crosslaps above baseline values for two years, and a decrease of BMD values. This rebound effect is associated with spontaneous clinical vertebral fractures (SCVF) in close to 15% of patients considering a follow-up of 2 years without taking another osteoporosis treatment. We report the clinical characteristics of 31 patients evaluated at our center from July 2015 to January 2018.
Results
Thirty women and one man, 62.8 ± 10.1 years, experienced 145 SCVF (median 5) in the 11.7 ± 3.0 months (median 11; min 7, max 20) following the last denosumab injection. They received 6.4 ± 2.7 denosumab injection (min 2; max 11). Ten women had vertebroplasties with 22 new SCVF in the following days. Nine women received aromatase-inhibitors (AI) with denosumab. Eight women had prevalent VF, five received bisphosphonate before denosumab. The mean B-crosslaps value at the time of SCVF was 1511 ± 573 µg/l; B-crosslaps values increase with the number of denosumab doses ($P = 0.05$) and decrease with age ($P < 0.01$). The number of SCVF was inversely associated with age ($P < 0.004$). Before the vertebroplasty, the mean number of SCVF was 5.1 ± 3.0 vs 2.3 ± 1.5 in women <65 vs >65 years. The delay between DD and the occurrence of SCVF increases with age: 10.6 ± 1.6 vs 13.3 ± 3.8 months, before vs after 65 years ($P < 0.01$). The mean reasons for DD were: end of AI or no more osteoporosis (15), omission (7), patient's wish (5), AFF or dental intervention (4).
Conclusion
The SCVF are a very severe and frequent clinical complication occurring after DD. A close follow-up during 2 years post DD is necessary. Studies are urgently needed to better define the place of denosumab in osteoporosis treatment, and the strategies to avoid these side effects.

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GP60

Effects of anti-osteoporotic medications on glucose metabolism and the incidence of type 2 diabetes mellitus: a systematic review

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Introduction
Type 2 diabetes mellitus (T2DM) and osteoporosis may co-exist in the same individual. However, the exact effect of anti-osteoporotic treatment on glucose metabolism is unknown. We aimed to systematically review the effects of anti-osteoporotic medications on glucose metabolism and the incidence of T2DM.
Methods/design
PubMed, Cochrane and EMBASE were systematically searched until the 31 of December, 2017.
Results
Bisphosphonates ($n = 2$): One retrospective cohort study ($n = 35\,998$, follow-up: 42 months) showed a significant reduction in T2DM risk in individuals exposed to bisphosphonates, compared with age-, sex- and body mass index (BMI)-matched controls. The other retrospective cohort study ($n = 23\,976$) did not show any significant effect (follow-up: 4.2 years).
Alendronate ($n = 3$): In one randomized placebo-controlled trial (RCT), no difference in fasting plasma glucose (FPG) concentrations or T2DM incidence was observed between postmenopausal women assigned to alendronate ($n = 3084$) or placebo ($n = 3067$), after four years. In one retrospective case-control ($n = 1011$) and one cohort study ($n = 55\,090$), patients exposed to alendronate showed a reduced incidence of T2DM, compared with no treatment (mean time of exposure: 3.8 years).
Zoledronic acid ($n = 2$): One RCT ($n = 3537$, follow-up: four years) and one prospective study ($n = 24$, follow-up: 1 year) did not show any effect on glucose metabolism in non-diabetic osteoporotic postmenopausal women.
Denosumab ($n = 3$): One RCT ($n = 3535$, follow-up: three years) and two prospective studies ($n = 38$ and $n = 14$, follow-up: 24 and 12 weeks, respectively) did not show any effect on FPG or T2DM incidence.
Teriparatide ($n = 3$): One study ($n = 23$) showed an increase in FPG and insulin resistance (IR), after six months of treatment. Two other prospective studies ($n = 14$ and $n = 25$) did not show any effect.
Strontium ranelate ($n = 1$): One study ($n = 40$, follow-up: 12 months) did not show any effect on FPG.
Raloxifene ($n = 17$). Only one prospective study in T2DM ($n = 37$, follow-up: six months) showed a decrease in HbA1c levels. Two RCTs in non-diabetic patients ($n = 44$ and $n = 30$, follow-up: two and six months, respectively) showed a decrease in FPG and IR.
Bazedoxifene ($n = 1$): One prospective study ($n = 20$) did not show any effect in T2DM patients, regarding FPG or IR after 12 weeks of treatment.
Conclusions
Bisphosphonates and raloxifene exert either neutral or beneficial effects on glucose metabolism. Neutral or detrimental effects have been reported for teriparatide. Neutral effects have been also observed with denosumab, basedoxifene and strontium ranelate, although these data derive mainly from small prospective studies of short duration. The reduction in T2DM risk with bisphosphonates warrants further investigation.

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GP61

Bone structural components and lean mass assessed by 3D-DXA in hip fracture patients

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Bone mass, macrostructure and lean mass are being identified as main contributors of strength of upper femur. The purpose of this study has been to assess the role of the cortical and trabecular bone as well as muscle mass in the hip fracture production. We used a new DXA application which allow 3D bone volume reconstruction from standard 2D DXA scans, providing a three dimensional approach of the femoral shape and bone density spatial distribution and measurement cortical thickness. The purpose of this study was to analyze these measurements in a cohort of elderly patients suffering a recent hip fracture.

Methods
A prospective study was carried out to collect scans from 96 patients of both sexes, older of 75 years, who have suffered a hip fracture indoor in a shorter interval of 2 weeks. None of the patients had osteoporotic fracture history at baseline. 3D-DXA technology in an early version (Galgo Medical S.L; Barcelona, Spain) was used to obtain patient-specific models from the 2D-DXA scans performed in the opposite femur (iDXA model GE Healthcare). The 3D-DXA algorithm made the registration of a 3D appearance model incorporating statistical information about the femoral shape and density onto the 2D DXA image. From the resulting patient-specific models the volumetric BMD can be automatically quantified as well as the volume (for trabecular and cortical regions) and cortical thickness distribution. Also, a total body scan was performed in these patients for body composition analysis purpose. The parameters were compared with reference values obtained on age and sex matched healthy volunteers and also on young people of same sex.
Results
A 47.1% of these patients were classified as osteoporotic using the WHO criteria. The femur of the patients suffering hip fracture show a significant less vBMD and BMC in cortical and trabecular bone ($P > 0{,}001$). The average cortical thickness was also lower for fracture group (1.49 mm) than for sex and age-matched references (1.63 mm, $P < 0.001$). This difference was bigger (26%) at the antero-superior radiant of femoral neck. The limb lean mass had a good correlation with all the bone parameters (r2: 0.218–0.375). Trabecular bone parameters (vBMD, BMC) were the most deviated from reference values.
Conclusion
Both trabecular as well as cortical bone assessed by 3D-DXA are decreased in patients suffering hip fracture.

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GP62

Inflammatory profile in monocytes of patients with Addison's disease and Vitamin D effects

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Introduction
Vitamin D (VD) deficiency affects many autoimmune disorders requiring steroid therapy. In contrast to glucocorticoid immune suppressive doses for autoimmune diseases, patients with Addison's disease (AD) require physiological replacement. There is growing evidence of a cross-talk between glucocorticoids (GC) and VD. However, VD's interaction with the GC pathway remains poorly understood.
Methods
To explore this issue, $CD14^+$ monocytes were obtained from 15 Addison patients and 30 healthy controls (HC). Cells were stimulated with VD and/or IL1β as an inflammatory stimulant for 24 h. To address inflammatory responses, gene expression levels of anti-inflammatory interleukin 10 (IL-10), programmed cell death ligand 1 (PD-L1) and VD receptor (VDR) were analyzed by qPCR and normalized to endogenous reference 18sRNA.
Results
The mRNA expression of IL1β-induced VDR was reduced after VD addition in AD patients and HC ($AD_{IL1\beta/IL1\beta+VD}$ 343 vs 205, $P = 10^{-4}$; $HC_{IL1\beta/IL1\beta+VD}$ 307 vs 213, $P = 2\times10^{-4}$). IL-10 expression in AD patients showed a higher expression compared to HC in the culture conditions (untreated, IL1β, VD) and baseline $CD14^+$ monocytes (Baseline $P = 0.05$, untreated $P = 0.03$, IL1β $P = 0.0007$, VD $P = 0.007$). No difference of IL-10 expression between HC and AD was observed in IL1β + VD culture condition ($P = 0.4$). However, HC showed a strong activation of IL-10 expression after VD addition in IL1β-treated monocytes, whereas no activation of IL-10 could be observed after VD addition in IL1β-stimulated monocytes in AD patients ($AD_{IL1\beta/IL1\beta+VD}$ 134 vs 126, $P = 0.7$, $HC_{IL1\beta/IL1\beta+VD}$ 76 vs 126, $P = 2\times10^{-5}$). PD-L1 expression did not differ from HC, however, it increased after VD addition in IL1β-stimulated monocytes in HC, but only marginally in AD ($AD_{IL1\beta/IL1\beta+VD}$ 12 vs 14, $P = 0.06$, $HC_{IL1\beta/IL1\beta+VD}$ 16 vs 23, $P = 0.006$).
Conclusion
VD-induced downregulation of VDR implies a functional feedback mechanism of VDR, indicating a normal paracrine cellular regulation of VD in both AD patients and HC. Regarding anti-inflammatory parameters we showed an increased IL-10 expression in AD patients, which could be explained by their GC replacement therapy that may affect the immune response more than the endogenous cortisol of healthy individuals. Furthermore, the observation that anti-inflammatory cytokines IL-10 and PD-L1 do not respond to VD stimulation in AD patients may indicate a cross-inhibition of VD and GC potentially leading to an attenuation of the inflammatory response.

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Cardiovascular

GP63

OCT1 gene variants are associated with cardiovascular characteristics in non-diabetic, prediabetic and diabetic patients

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Type 2 diabetes (T2DM) patients are at high risk for vascular complications. Some of them have even a higher risk during metformin therapy, as we have recently shown by associations of polymorphisms in the Oct1 gene with a therapy-dependent increased risk of cardiovascular death. In this study, we investigated whether Oct1 gene variants were associated with cardiovascular characteristics such as pulse wave velocity (PWV), echocardiographic parameters and intima/media thickness (IMT) in non-diabetic, prediabetic and T2DM patients at cardiovascular risk. Data from the BioPersMed cohort ($n = 1025$), a prospective cohort study of asymptomatic patients at cardiovascular risk, were analysed. T2DM, prediabetes and absence of diabetes (non-diabetics) were defined according to ADA criteria. Determination of Oct1 genotypes was done by GSA array (Illumina Inc., USA), pulse wave analysis by a SphygmoCor device (Atcor Medical, Australia), and carotid intima/media thickness as well as echocardiographic measurements were performed using the Vivid 9 device (GE Healthcare Austria GmbH & Co OG, Austria). In a preliminary analysis, we focused on associations with score systems for cardiovascular risk (PROCAM and Framingham), as well as PWV and IMT. An association with the Framingham score was found for SNPs rs35888596 ($P = 0.012$) and for rs112476023 ($P = 0.015$) in nondiabetics and for rs461473 ($P = 0.018$) and rs806383 ($P = 0.03$) in prediabetics. PROCAM score was associated in non-diabetics with rs112476023 ($P = 0.023$) and in T2DM with rs662138 ($P = 0.045$). A significant association with PWV was seen for rs12208357 ($P = 0.02$) in non-diabetics, for rs12208357 ($P = 0.009$) in prediabetics and for rs662138 ($P = 0.034$) in T2DM. Associations with IMT were documented in T2DM for rs806383 ($P = 0.034$), rs2197296 ($P = 0.027$), rs622342 ($P = 0.008$), as well as for rs662138 ($P = 0.030$), in prediabetics for rs34130495 ($P = 0.048$) and rs622342 ($P = 0.049$) and in T2DM for rs2282142 ($P = 0.008$), rs2282143 ($P = 0.009$) and rs112476023 ($P = 0.019$). According to these associations, several variants in the OCT1 gene might play a consistent role in the modulation of vascular properties and concomitant cardiovascular characteristics and thus contribute to an increased cardiovascular risk even beyond the occurrence of diabetes or therapy options.

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GP64

Habitual dietary intake of n-3 polyunsaturated fatty acids and leptin gene expression in visceral and subcutaneous adipose tissues of non-diabetic adults

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Introduction and aim
Leptin is a hormone that mainly expressed and secreted in adipose tissues and has a number of important effects on regulation of body weight, energy expenditure, and thermogenesis. High intake of n-3 polyunsaturated fatty acids (PUFA) promotes reduced plasma concentration of triacylglycerol, glycerol, and free fatty acids, as well as metabolism of the epididymis. The aim of current study was to examine the association of n-3PUFA on leptin gene expression in visceral and subcutaneous adipose tissue of adults.
Methods
We gathered visceral and subcutaneous adipose tissues during an elective abdominal surgery which have minimal impact on dietary intake form 98 participants aged >19 who were free of diabetes and cancers and without using anti-lipid medication. Before the surgery, a reliable and validated semi-quantitative food frequency questionnaire was completed to assess habitual dietary intake of n-3 PUFA, α-linolenic acid ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Dietary exposures were adjusted for energy by using the residual method. The mRNA expressions of leptin gene in both adipose tissues measured by SYBER-Green real-time quantitative PCR. Multivariable linear regression was performed to assess the association of dietary n-3 PUFA with leptin gene expression. All models were adjusted for age, body mass index(BMI), insulin, and physical activity.
Results
The mean age of participants was 41.6 years and BMI was 33.6 kg/m^2. Median intake of n-3 PUFA in our study was 2.44 g/day which corresponded to 0.88% of total energy intakes. In visceral fat, leptin mRNA levels were significantly higher compared with subcutaneous adipose tissue. After controlling for confounders, usual intake of dietary n-3 PUFA was negatively associated with leptin gene expression in subcutaneous ($\beta=-0.523$, $P<0.001$) and visceral ($\beta=-0.780$, $P<0.001$) adipose tissues. Moreover, we found a significant inverse association of dietary intake of ALA ($\beta=-0.695$, $P<0.001$) and DHA ($\beta=-0.471$, $P=0.009$) with leptin gene expression in visceral adipose tissue. There was no significant association between leptin gene expression and EPA intake.
Conclusion
The current study illustrated that higher usual dietary n-3 PUFA were negatively associated with leptin gene expression in both adipose tissues independent of BMI, age, insulin, and physical activity. In addition, DHA and ALA had a relationship with leptin mRNA expression, especially in visceral adipose tissue. It seems that habitual intake of n-3 PUFA might affect adipose tissue metabolism through modifying leptin gene expression.

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GP65

Decreased heart rate variability can predict future development of metabolic syndrome in Asian adults

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Introduction
This study aimed to examine whether altered Heart Rate Variability (HRV) could predict the risk of development of metabolic syndrome (MetSD) in Asians.
Methods
We investigated health checkup records of 33 752 adults aged 20–65 years old who did health checkups and HRV measurement between April 2011 and June 2014 at Kangbuk Samsung Hospital, without MetSD, anemia, thyroid disease, malignancy, and heart disease. A 3-minute HRV recording was performed while seating on a chair. We analyzed HRV in time domain (standard deviation of the normal-to-normal interval [SDNN, ms], root mean square difference [RMSSD, ms]), and frequency domain (total power [TP, 0–0.4 Hz, ms^2], very low-frequency [VLF, $\leq$0.04 Hz, ms^2], low-frequency [LF, 0.04–0.15 Hz, ms^2], high-frequency [HF, 0.15–0.4 Hz, ms^2] power, normalized LF, normalized HF, and LF : HF ratio). We compared the risk of incident MetSD between 2012 and 2016 using multivariate Cox analysis according to tertiles of HRV variables with tertile 1 as reference group. MetSD was determined by the presence of three or more of waist circumference $\geq$90 cm in men or $\geq$85 cm in women, fasting glucose $\geq$100 mg/dl or use of an anti-glycemic agent, triglyceride >150 mg/dl or use of an antihyperlipidemic agent, high-density lipoprotein-cholesterol <50 mg/dl in men, <40 mg/dl in women or use of an anti-hyperlipidemic agent, and blood pressure $\geq$130/85 mmHg or use of an antihypertensive drug.
Results
Mean age of subjects were 37.8$\pm$5.7 years. During 40 324 033 person-years, 4061 subjects were diagnosed with MetSD. Most of time and frequency domain variables were lower in MetSD group than nonMetSD group, whereas LF norm and LF/HF ratio were higher. In cox analysis, the risk of development of MetSD was significantly decreased as SDNN, RMSSD, TP, VLF, LF, HF, and HF norm tertiles increased. In case of LF norm and LF/HF ratio, positive relationship was observed. These tendencies were maintained in RMSSD, LF, and HF after adjustment for age, sex, body mass index, current smoking, systolic blood pressure, serum low-density lipoprotein-cholesterol, high sensitivity c-reactive protein, and glucose levels as confounders. Hazard ratios(95% confidence intervals) of tertile 3 were 0.83(0.76–0.91) for RMSSD, 0.92(0.85–0.99) for LF, and 0.90(0.82–0.98) for HF.
Conclusion
Decreased HRV can anticipate the risk of incident MetSD in young Asian adults.

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GP66

Evaluation of irisin levels in chronic heart failure with preserved or reduced ejection fraction

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Background
The recently discovered myokin Irisin, a peptide originated by a proteolytic cleavage of the transmembrane protein fibronectin type III domain containing 5 (FNDC5) whose expression is induced by exercise and/or by increasing peroxisome proliferator-activated receptor (PPAR)-γ co-activator 1α (PGC-1α), has been considered a prognostic factor in Chronic Ischemic Cardiomyopathy and Acute Heart Failure. Nevertheless, no data are available on Irisin levels in Chronic Heart Failure, both with preserved (HFpEF) or reduced (HFrEF) ejection fraction, matched for age and NYHA classes.
Materials and methods
Therefore, we have evaluated basal plasma irisin levels, by immunoenzymatic method, in these two subtypes of Heart Failure ($n=22$ HFpEF, age range 59–88 years, mean$\pm$S.E.M. BMI 28.9$\pm$1.3 kg/m^2; $n=18$ HFrEF, 54–88 years, BMI 26.5$\pm$0.9) and correlated them with metabolic parameters (HOMA-index) and Total Antioxidant Capacity (TAC), as a parameter of Oxidative Stress, measured with a spectrophotometric method, using the system H_20_2-metmyoglobin and the chromogen ABTS.
Results
The two groups did not show significant differences in NT-proBNP levels (2548.8$\pm$551.1 ng/ml in HFpEF vs 6007.1$\pm$2297.2 in HFrEF). Fasting Irisin levels were significantly lower in HFrEF (mean$\pm$S.E.M. 2.77$\pm$0.77 ng/ml) in respect to HFpEF (mean$\pm$S.E.M. 7.72$\pm$0.76 ng/ml). Moreover, a significant inverse correlation between Irisin and LAG values in HFpEF was found ($r^2=0.145$, $P<0.05$). On the contrary, in HFrEF patients, Irisin and LAG presented a trend toward direct correlation although not significant. No others correlations was found between Irisin and BMI or HOMA-IR for both HFrEF and HFpEF groups.
Conclusions
These data may suggest a different pathophysiological mechanism in these two subtypes of CHF, and a possible role of Oxidative Stress in modulation of Irisin levels. They also strengthen the involvement of metabolic factors in HFpEF.

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GP67

Liraglutide prevented the deposition of Collagen in the animal model of Bleomycin-induced lung fibrosis

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Idiopathic pulmonary fibrosis (IPF) is an excessive accumulation of fibrous filaments in the extracellular matrix (ECM), in response to an inflammatory reaction that disrupts normal lung architecture and physiology. Collagen is the most abundant fibrous protein in the ECM. The GLP-1 receptor is highly expressed on lung tissue, where his activation plays an essential role in the synthesis and secretion of surfactant proteins. The objective of this study was to elucidate the effect of Liraglutide treatment on collagen synthesis and deposition in the lungs of an animal model of IPF. IPF was induced in male rats by a single intra tracheal instillation of bleomycin (BLM, 2.5 mg/kg) on day 0. Animals were treated with Liraglutide at a dose of LIR, 100 μg/kg per 12 h subcutaneous, using two different protocols. 1-Preventive treatment: LIR treatment was given from day-1 to day 6 and animals were sacrificed in day 7 and day 21. 2-Therapeutic intervention: animals were treated from day 10 to day 20 after BLM; and animals were sacrificed on day 21. Lung lobes were isolated and frozen for mRNA expression analysis by Real time PCR, and for hydroxyproline quantification and Arginase-1 activity testing. We obtained Broncho alveolar lavage liquid for analysis of soluble collagen. The mRNA expression of Collagen type 1 and the enzymes Arginase-1 and prolyl hydroxylase, which are essential for collagen fibre synthesis, were increased at day 7 and day 21 in BLM instilled animals. Tissue levels of hydroxyproline were very increased just at day 21, in the fibrotic phase. LIR treatment normalized the mRNA expression levels of the two enzymes at the times studied. In addition, LIR administration decreased day 21 type I collagen mRNA expression and total collagen deposition on lung tissue, as well the soluble collagen in alveolar lavage liquid. In conclusion, incretins play an important role in the regulation of the synthesis and activity of key enzymes in the formation of collagen fibres and deposition. Since, incretins may be useful molecules in the treatment and prevention of the pulmonary tissue fibrotic processes.

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GP68

Turner syndrome and cardiovascular risk

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Introduction
Turner Syndrome (TS) is associated with cardiovascular anomalies and account for a threefold higher mortality in these women. The most common findings are congenital malformations of the heart (CMH), aortic dissection, valvular heart disease (VHD), hypertension and ischemic heart disease. It has been suggested that the ocurrence of cardiovascular disease in TS women is related to their karyotype and possibly to growth hormone (GH) treatment. Our study aimed to assess cardiovascular risks in patients with TS.
Methods/design
This was a retrospective study of 64 patients with TS identified from our institutional database. They were categorized in three groups, according to their karyotype: group 1 included 24 patients with monosomy X, group 2 comprised 21 patients with mosaicism, and group 3 comprised 19 patients with structural aberrations of X chromossome. We assessed age, treatment with GH, pubertal development, lipid profile, diabetes mellitus, body mass index, blood pressure and cardiac and valvular abnormalties. The association between variables was evaluated using Fisher's exact test and paired samples *t* test.
Results
The patients evaluated were aged 23–69 years old (s.d. 36 ± 10.1), with median follow-up time of 20 ± 8.3 years. VHD was present in 19 patients (30%) and CMH were detected in 17 patients (27%), the most common being aortic coarctation ($n=11$). CMH were detected more frequently in group 1 patients ($P=0.001$), namely aortic coarctation (8 of the 11 cases detected, $P=0.001$). Group 2 patients presented a higher rate of spontaneous puberty than the others ($P=0.029$). There were no differences regarding other cardiovascular risk factors and anomalies among the 3 groups, as well as association between GH treatment and the development of CMH or VHD.
Conclusion
The pathophysiology of the cardiovascular anomalies in TS is still unclear. In our study, monossomy X was associated with CMH and spontaneous pubertal development was associated with VHD. Life-long surveillance is recommended, namely evaluation of cardiac function, aortic diameter and blood pressure, in order to provide early identification and management of potentially serious cardiovascular conditions.

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GP69

Can monogenic severe hypertriglyceridemia be differentiated from polygenic forms through clinical features: data from APPROACH and COMPASS studies in FCS and non-FCS hypertriglyceridemic patients?

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Introduction
Differentiation between familial chylomicronemia syndrome (FCS), a rare hypertriglyceridemia, and severe hypertriglyceridemia (sHTG; non-FCS) is challenging due to overlap in triglyceride (TG) levels and symptomology but important in disease management. Clinical characteristics that allow for reliable differentiation may exist in the presenting clinical features and primary diagnostic testing. The objective of this analysis was to assess whether readily obtainable clinical information can effectively diagnose and differentiate patients with FCS from sHTG (non-FCS) based on 2 well-curated datasets arising from 2 clinical studies.
Methods
Patients from two Phase-III clinical trials of sHTG patients, one with molecularly-proven FCS and one with polygenic sHTG (non-FCS) were included in this analysis. Logistic regression analyses were performed to determine the ability of variables (individually or sets), including patient demographics, medical history and baseline lipids, to differentiate between FCS and sHTG (non-FCS) populations. For each of the logistic regression analyses, receiver operating characteristics (ROC) were employed to determine the highest accuracy (defined as the percentage of times the Actual and Predicted values match) using the predicted probability (Pr) of being in the FCS-population. Positive predictive-value (PPV), and negative predictive-value (NPV) are defined as follows: PPV is Pr (Predicted-FCS + True-FCS |Predicted-FCS); NPV is Pr(Predicted Non-FCS + True Non-FCS|Predicted Non-FCS). Optimal was defined as maximizing sensitivity + specificity.
Results
One hundred and fifty four patients ($n=49$ genetically confirmed FCS patients and $n=105$ sHTG (non-FCS) patients) were included in the analysis. Of the 154 patients, 45/49 of FCS patients and 99/105 of sHTG (non-FCS) patients were diagnosed correctly based on the model. Optimal sensitivity was 91.8%, optimal specificity was 94.3%, and accuracy was 93.5%. Fasting low-density lipoprotein-Cholesterol (LDL-C), apolipoprotein-A1 (apoA1), and apoB were determined to have the highest individual predictability with ROC area-under-the-curve values of 0.902, 0.8971, and 0.8852, respectively. FCS and sHTG (non-FCS) patients could be differentiated with an accuracy of 91.6% with a 3-variable set (apoB/LDL-C, BMI, and history of pancreatitis) and 93.5% with a 5-variable set (HDL-C and VLDL-C included). Individual variables and sets both had higher NPV than PPV.
Conclusions
Our results indicate that FCS and sHTG (non-FCS) patients can be diagnosed and differentiated with a high-degree of accuracy by analyzing readily obtainable clinical information. This suggests that where genetic testing is not available or among FCS patients who do not test positive for a known genotype, the diagnosis of FCS can be made clinically with a high-degree of certainty.

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GP70

Changes in lipid profile 5 years after bariatric surgery: laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy

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Importance
Few studies have compared mid-term results of laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy and none have focussed on lipid profile.
Objectives
The main objective of this study was to compare laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy with respect to 5-year remission rate of the different lipid disturbances. Secondary outcomes included relapse, late remission and incidence rates of the different lipid disorders and evaluation of factors associated with mid-term remission. Design, setting and participants: A retrospective analysis of a non-randomised prospective cohort was conducted on patients with severe obesity undergoing bariatric surgery at Hospital del Mar, Barcelona, from January 2005 to January 2012 with $\geq$ 5 years follow-up.
Exposure
Laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy. Main outcome: 5-year remission rate of lipid disorders after laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy.
Results
87% of the patients were women, mean age of the total cohort was 46.1 ± 8.7 years and BMI 45.2 ± 4.8 kg/m^2. Of the 259 patients who underwent bariatric surgery between 2005 and January 2012, 151 completed 5 years follow-up. The 5-year remission rate of high low-density lipoprotein cholesterol was superior after laparoscopic Roux-en-Y gastric bypass with respect to laparoscopic sleeve gastrectomy [61.2% (30/49) versus 26.1% (6/23); $P=0.011$] being male sex, absence of statins treatment and type of bariatric surgery technique (laparoscopic Roux-en-Y gastric bypass) the associated factors with remission. Hypertriglyceridemia remission was also higher after laparoscopic Roux-en-Y gastric bypass [92.0% (23/25) versus 66.7% (10/15); $P=0.041$], although type of surgery was not an associated factor. No differences were found in remission rates of low high-density lipoprotein cholesterol between groups. Absence of fibrates treatment and 5-year percentage of excess weight loss were independently associated with hypertriglyceridemia remission and only the latter was independently associated with low high-density lipoprotein cholesterol remission 5 years after surgery.
Conclusions
Five-year outcome data showed that, among patients with severe obesity undergoing bariatric surgery, laparoscopic Roux-en-Y gastric bypass was more effective than laparoscopic sleeve gastrectomy in terms of total and low-density lipoprotein cholesterol reduction and remission, with no differences in hypertriglyceridemia and high-density lipoprotein cholesterol normalization.

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Diabetes Complications

GP71

Prevalence and risk factors of periodontitis in diabetic patients with or without metabolic syndrome

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Introduction
This study examined prevalence and risk factors of peri-odontitis in representative samples of Korean adults, with and without diabetes mellitus (DM). Additionally, we did subgroup analysis in diabetic patients with or without metabolic syndrome.
Methods
This study analyzed data from the 2010 to 2015 the Korea National Health and Nutrition Examination Survey (KNHANES) in South Korea which include periodontitis and the parameter of metabolic syndrome (MS). MS was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III). Among data collected from 22,737 respondents, propensity score matching of sex and age was applied and the data were analyzed.
Results
A total of 4706 subjects after propensity score matching of sex and age, including 2060 with periodontitis and 2646 without periodontitis, were analyzed. Periodontitis was present in 43.7% of the total. When compared to the no periodontitis group, the periodontitis group was older (63 ± 10.4), had more males (58.8%), a lower number of subjects who had higher education (56.3%), low-income families (32.1%), higher fasting plasma glucose (122.3 ± 39.2), and higher waist circumference (86 ± 9). Moreover, systolic blood pressure, body mass index, and plasma triglycerides were higher in the periodontitis group whereas HDL cholesterol was lower ($P<0.001$). Many of those in the periodontitis group had hypertension (57.6%) and diabetes mellitus (55.5%), and metabolic syndrome (46.3%). It showed the same tendency more like in diabetes group. In multiple regression analysis of the risk factors of periodontitis, the risk increased when MS was present (OR 1.12, 95% CI 1.01–1.24), when diabetes mellitus was present (OR 1.19, 95% CI 1.02–1.38), and when there was history of smoking (OR 1.63, 95% CI 1.46–1.81). In particular, for MS in DM, the risk of periodontitis increased as the number of MS components became higher ($P<0.001$).
Conclusion
The risk of periodontitis was 1.19-fold higher when DM was present than when it was not. The risk was particularly higher when MS was also present and in those that smoke. Moreover, the risk of periodontitis also increased as number of the MS components became higher. Thus, diabetic patients with periodontitis may benefit when they control metabolic parameters.
Keyword: Diabetes mellitus, metabolic syndrome, periodontitis, korean national health and nutrition examination (KNHANES)

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GP72

Toe-brachial index is associated more strongly with progression of diabetic nephropathy than ankle-brachial index in type 2 diabetic patients

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Background and aims
Atherosclerosis is more prevalent among people with chronic kidney disease (CKD) than among those with normal renal function. Ankle-brachial index (ABI) and toe-brachial index (TBI) are a simple useful method for assessing peripheral atherosclerosis. The aim of our study was to investigate whether ABI or TBI were more strongly associated with progression of diabetic nephropathy such as change of urinary albumin/creatinine ratio (ACR), serum creatinine levels and estimated glomerular filtration rate (eGFR).
Materials and methods
We recruited a total of 149 type 2 diabetics: 62 men (mean age 62.4 ± 12.1 years) and 87 women (mean age 60.3 ± 10.9 years) with CKD ($\geq$ stage 2) by diabetic nephropathy and followed for 1.6 ± 1.2 years. Renal function was evaluated by serum creatinine levels, estimated eGFR (Cockcroft-Gault equation) and urinary ACR. Baseline-to-study end changes in eGFR were calculated, and yearly change of eGFR (ml/min/year) was computed. ABI and TBI measurements were performed with the subject in a supine position, and were determined as the ratio of ankle or toe systolic blood pressure to the brachial systolic blood pressure, with both determined using an automatic device.
Results
Overall, the mean age was 61.2 ± 11.0 years, duration of diabetes 13.8 ± 10.5 years, HbA_{1C} $7.9 \pm 2.2\%$, ACR $1{,}635.2 \pm 783.3$ mg/gCr, and serum creatinine 1.6 ± 1.1 mg/dL. Mean calculated GFR was 62.8 ± 27.1 ml/min/1.73m^2. ABI were 1.05 ± 0.24 (Rt.) and 1.01 ± 0.20 (Lt.). TBI were 0.73 ± 0.31 (Rt.) and 0.79 ± 0.22 (Lt.). Of the study population, 39 patients (26.1%) were smokers or ex-smokers, 135 patients (90.6%) were having hypertension, and 123 patients (82.6%) were taking ACEI or ARB. Age, duration of diabetes, serum creatinine, ACR and eGFR were significantly correlated with ABI or TBI. Mean yearly change of eGFR was 7.2 ± 10.4 ml/min per year. Yearly change in the eGFR was negatively correlated with TBI, but not with ABI. Changes of ACR or serum creatinine were not significantly correlated with ABI or TBI. By Univariate linear regression, TBI but not ABI showed a significant negative correlation with yearly change in the eGFR ($r=-0.309$, $P<0.05$).
Conclusion
This study demonstrated that TBI may be predictor of progression of diabetic nephropathy in patients with type 2 diabetes. We suggest that toe-brachial index may help to manage appropriately as early predictors on progression of diabetic nephropathy.

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GP73

The BMI and skeletal muscle mass as a risk factor of carotid atherosclerosis in patients with type 2 diabetes

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Background
The body mass index (BMI) is the most widely used method of assessing fat accumulation, and is recognized as an independent risk factor for cardiometabolic diseases. However, there might be substantial variations in the fat or muscle amount among persons with a similar BMI. The aim of the present study was to investigate whether BMI and skeletal muscle mass (SMM) estimated from by bioelectrical impedance analysis (BIA) are associated with carotid atherosclerosis in patient with type 2 diabetes.
Methods
This was an observational study performed in 4437 patients with type 2 diabetes. Anthropometric measures and BIA were performed for each subject. Carotid atherosclerosis was defined by having a clearly isolated focal plaque or mean carotid intima-media thickness (CIMT) $\geq$ 1.1 mm.
Results
CIMT and the frequency of carotid atherosclerosis were higher with decreasing SMM quartiles rather than with increasing BMI quartiles in both genders. The SMM to BMI ratio was significantly related with CIMT and carotid atherosclerosis in both genders, even after adjusting for potential confounders (adjusted odds ratio of carotid atherosclerosis for the highest quartile of this ratio compared with the lowest quartile being 0.630 [95% CI, 0.440–0.901] and 0.582 [0.391–0.860] in men and women, respectively).
Conclusions
BMI alone could not assess the carotid atherosclerotic risk. An additionally estimation for skeletal muscle may provide a role in assessing atherosclerotic burden in patients with type 2 diabetes.

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GP74

Is liver stiffness associated with diabetic complications in patients with type 2 diabetes and non-alcoholic fatty liver disease?

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Aim
Non-alcoholic fatty liver disease (NAFLD) and type 2 Diabetes (T2D) are common conditions that frequently co-exist. Studies have shown an increase likelihood of micro and macrovascular complications in this population, as well, as an increased risk of developing more severe forms of liver disease. The aim of this study was to identify diabetic complications in patients with both diseases and search for an association with liver stiffness assessed by Liver Elastography (LE).
Methods
We retrospectively reviewed patients with T2D and NAFLD (May 2016-December 2017) after excluding other causes of liver disease and in whom LE was performed (LE $\geq$8.2 kPa reflects fibrosis, LE $\geq$9.9 kPa reflects significant fibrosis).
Results
We reviewed 555 patients, 25% (139) had NAFLD. 33.8% (47) of the patients with NAFLD had T2D, and up to 73.4% (102) had T2D or Prediabetes. In the T2D population, 68.1% (32) were men between 39-81 years old (60.1$\pm$8.7) with 6.02$\pm$4.99 years of evolution. 85.1% had metabolic syndrome: 97% BMI $\geq$25 kg/m^2, 76.6% dyslipidemia, 70.2% high blood pressure, 21.3% OSAS and 17% hyperuricemia. 80.8% had ALT> AST, and 48.9% ALT $\geq$40 IU/L. Liver fibrosis assessed by LE was present in 29.8% of the patients, 20% had significant fibrosis. A positive correlation was found between kPa and glomerular filtration rate (CKD-EPI) (r=0.331, $P\leq$0.05), and liver stiffness increased as glomerular function worsened (P=0.008). However, we did not find an increased prevalence of diabetic retinopathy nor diabetic neuropathy in patients with fibrosis. Patients with fibrosis had a higher non-significant prevalence of peripheral artery disease, carotid obstruction and cardiovascular events in comparison with the group without fibrosis (P=0.595, P=0.154, P=0.241, respectively). No increased prevalence of cerebrovascular events was found in patients with liver fibrosis.
Conclusions
Liver fibrosis is highly prevalent in patients with NAFLD and T2D. Increased liver stiffness is significantly associated with renal dysfunction in T2D and a higher non-significant prevalence of cardiovascular events was found in this population. Thereby, our results support the value of LE and the assessment of individual cardiovascular risk in every patient with T2D and NAFLD.

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GP75

Effects of post-transplant and pre-existing diabetes mellitus on graft function after kidney transplantation

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Diabetes mellitus (DM) is one of the most serious comorbidities in kidney transplant recipients. New onset diabetes after kidney transplantation (NODAT) is a common and an important complication following solid organ transplantation. It is associated with poor graft function and increased cardiovascular complications. Therefore, management of hyperglycemia after transplantation is important to reduce diabetes-related risks. We aimed to compare the effects of pre-existing DM and NODAT on graft functions in kidney transplant recipients.
Methods
Fifty-nine kidney transplant recipients were divided into two groups: pre-existing diabetics (n=28, 52.7$\pm$10.2 years, 12 males) and NODAT (n=31, 49.9$\pm$11.8 years, 18 males). HbA1c and renal functions at the first year of transplantation and the last visit were obtained.
Results
The median post-transplant follow-up durations were 62.5 months in pre-existing DM group and 65 months in NODAT group. The median diagnosis time in NODAT group was 2.5 months (range: 1–159) after transplantation and thirteen recipients were diagnosed at the first month. There was no significant difference between gender, age, donor age, donor type and body mass index values in NODAT and pre-existing diabetics groups. Tacrolimus based immunosuppressive regimen ratios were significantly higher in NODAT group (61.3% vs. 29%, P=0.007). HbA1c levels (6.9$\pm$2 vs. 7.8$\pm$1.6%, P=0.036) at first year of transplantation were lower in NODAT group. HbA1c levels of both groups at the last visit were similar (7.49$\pm$1.7% in NODAT and 7.79$\pm$1.3% in pre-existing diabetics). Serum creatinine levels at the first year of transplantation (1.29$\pm$0.75 vs. 1.48$\pm$0.53 mg/dL) and at the last visit (1.67$\pm$1.58 vs. 2.14$\pm$1.63 mg/dL) were comparable in NODAT and pre-existing diabetics groups, respectively (P=0.056). Estimated glomerular filtration rate values at the first year of transplantation (69.5$\pm$27.2 vs. 56.0$\pm$29.7 mL/min/1.73 m^2, P=0.021) and at the last visit (61.0$\pm$27.7 vs. 42.7$\pm$21.2 mL/min/1.73 m^2, P=0.007) in NODAT group were significantly higher than those of pre-existing diabetics group. The ratio of graft lost in NODAT group was lower than that of the pre-existing diabetes group (6.5% vs. 14.3%, P=0.311).
Conclusion
Although glycemic control was achieved in both groups in our study, the presence of pre-existing diabetes was a risk factor for graft failure after kidney transplantation. Therefore, longer diabetes duration could negatively affect graft function in recipients with pre-existing diabetes.

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GP76

Glucose variability and pregnancy outcomes in gestational diabetes mellitus: a prospective study

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Introduction
Gestational diabetes mellitus (GDM) is associated with an increase of maternal-fetal complications. Continuous glucose monitoring system (CGMS) detects parameters of glycemic variability through which it could be predicted the appearance of maternal-fetal complications.
Methods
Women with GDM at 26–32 gestational weeks were allocated a 6-day CGM system (Ipro^{TM}2) right after diagnosis in an observational prospective study. It was analysed:
CGMS: mean glucose and standard deviation (S.D.), mean amplitude of glycemic excursions (MAGE), mean of daily differences (MOOD), continuous overlapping net glycemic action (CONGA). Expressed: mg/dl.
Maternal and neonatal outcomes.
Results
$n=52$. Maternal age 30 ± 2.42 years (>35 years$=40.3\%$), family history of diabetes 57.7%, prepregnancy BMI 26.1 ± 4.62 kg/m^2 (>30 kg/m$^2=23.1\%$), weigh gain 7.6 ± 5.19 kg, HbA1c 4.9%, insulin treatment 32.7%.
CGMS: mean 98.02, DS 19.66, MAGE 44.22 ± 13.16, MODD 19.44 ± 5.74, CONGA 86.19 ± 8.56.
Maternal and neonatal outcomes
Caesarean 32.7%, gestational age at delivery 39 week, macrosomia 9.6%, large for gestational age (LGA) 21.2%, small for gestational age 5.8%, neonatal hypoglycaemia 25%, neonatal hyperbilirubinemia 7.7% and need for supplemental oxygen in the neonatal 5.8%.
Multivariable binary logistic regression
MAGE was an independent factor for LGA (Odds ratio 1.075; 95% confidence interval 1.007–1.148; *P* value 0.031). It was not found another independent risk factor for maternal or neonatal outcomes.
Conclusions
There is a correlation between MAGE at diagnosis of GDM and LGA. The use of CGMS could identify patients with more risk of maternal-fetal complications. These patients should have a close surveillance in order to prevent complications. However, further studies with a larger number of patients are required.

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GP77

Patients with community acquired pneumonia are three times more likely to die if they have concomitant diabetes mellitus

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Objective
To compare the clinical features, mortality and morbidity outcomes in patients with diabetes mellitus and patients without diabetes mellitus, who are hospitalized with community acquired pneumonia (CAP).
Methods
This cross sectional study included 175 patients (49 patients with diabetes and 126 without diabetes) admitted with CAP to a tertiary care hospital. The study included both quantitative and qualitative variables, which were compared using Independent T test/Mann-Whitney Test (when the data sets were not normally distributed) and Chi-Square test/Fisher exact test respectively. Univariate regression was used to find the risk factors of mortality due to pneumonia in patients with diabetes and without diabetes. Multivariate analysis was used in the end to isolate the effect of diabetes for mortality in community acquired pneumonia (after excluding proven H1N1 cases) while controlling the effect of other variables.
Results
The mean age of presentation in patients with diabetes was 63.7 ± 10.9 years vs. 57.7 ± 16.6 years among patients without diabetes. (*P*-value-0.006). Comorbidities were present in 79.59% of patients with diabetes with heart disease as the most common comorbidity found in 53.06% of those with diabetes (*P* value-0.001). Other clinical features as well as outcome were not very much different in both the groups. On univariate analysis increasing capillary glucose at admission, a higher CURB 65 score, cigarette smoking, presence of type 1 respiratory failure, metabolic acidosis and requirement of invasive ventilation were associated with increased risk of mortality in patients with diabetes. On multivariate analysis diabetes mellitus was found to be a single independent predictor for mortality after controlling for age, COPD (by controlling respiratory acidosis and type 2 respiratory failure) and H1N1 infection with a *P* value of 0.045, an adjusted odds ratio of 2.344 with CI 1.02–5.382. Diabetes mellitus was an independent predictor for mortality in community acquired pneumonia (after excluding H1N1) with a *P* value of 0.008, adjusted odds ratio of 3.439 with a CI of 1.382–8.559.
Conclusion
Diabetes mellitus is an independent predictor of mortality in patients admitted with community acquired pneumonia.

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GP78

Diabetic patients are old as theirs feet are old:the strongest association of foot pathology with mortality in diabetes

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Background and aims
Foot lesions (amputations, ulcerations) are the consequence of neuro-vascular complications. Cardiovascular risk factors are similar for both. Thus, we carried out a prospective 5-year study to examine the effects of established complications and classical risk factors on mortality in diabetic patients.
Materials and methods
During the previous 5 years we analyzed 244 patients attending a diabetes clinic. The International Working Group on Diabetic Foot (IWGDF) risk categorization was used to quantify the severity of foot pathology. Retinopathy was diagnosed by funduscopy. Peripheral neuropathy diagnosed by the Neuropathy Disability Score (NDS) and Neuropad time to color change were studied as well. Coronary artery disease (CAD) and lower extremity arterial disease (LEAD)] were evaluated. Cardiovascular risk factors were: hypertension, triglycerides, HDLc, LDLc, diabetes duration, fibrinogen, proteinuria, smoking. 53 patients (group A) had meanwhile died, and 191 (group B) are still alive.
Results
There were no differences between groups A and B in the following parameters: male gender [31(58.5%) vs. 94(49.2%), $P=0.23$], diabetic retinopathy [34 (64.15%) vs. 105(54.97%), $P=0.29$], proteinuria (385.2 ± 609.9 vs. 443.9 ± 1003, $P=0.23$), CAD [5(9.43%) vs. 16(8.38%), $P=0.81$], [triglycerides (1.9 ± 1.51 vs. 1.93 ± 1.7 mmol/l, $P=0.90$), HDLc (1.27 ± 0.51 vs 1.25 ± 0.28 mmol/l, $P=0.80$), LDLc (3.44 ± 0.81 vs 3.62 ± 0.89 mmol / l, $P=0.18$)], [type 1 diabetes [6 (11.3%)). 24 (12.6%), $P=0.80$], HbA1c ($8.9\%\pm2.04$ vs. $9.2\pm1.94\%$, $P=0.17$)], smoking [7 (13.2%) vs. 36(18.8%), $P=0.34$]. Patients in group A exhibited significant differences in the following parameters: IWGDF risk category 2/3 ($P=0.0002$), VPT (3.35 ± 3.2 vs. 4.8 ± 3.00 V, $P=0.004$), Neuropad response (13.8 ± 8.9 $P=0.03$), age at developing foot lesions (69.2 ± 8.77 vs 66.2 ± 9.7 years, $P=0.03$), ankle reflexes (AR) score (3.42 ± 1.06 vs. 3.04 ± 1.28, $P=0.036$); among classical risk factors: hypertension [42(79.2%) vs. 117 (61.3%), $P=0.015$], fibrinogen (4.3 ± 1.11 vs. 3.89 ± 0.88, $P=0.02$), DM duration (20.2 ± 10.45 vs. 16.96 ± 8.8, $P=0.026$). However, in multivariable logistic regression analysis it was only IWGDF category 2/3 that remained significantly associated with mortality (OR: 3.78, 95% CI: 1.72–8.28, $P=0.001$).
Conclusion
This finding underlines the importance of timely diagnosis and management of diabetic foot pathology, especially when we are talking about the intensity of lowering HbA1c. The severity of diabetic foot pathology was a stronger prognostic factor of mortality than cardiovascular risk factors.

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GP79

Outcomes of hyperglycemia in patients with and without diabetes mellitus hospitalized for infectious diseases

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Context
Hyperglycemia is common among patients with and without diabetes mellitus (DM) hospitalized for infectious diseases. The long-term outcomes of hyperglycemia have not been adequately studied in this population.

Objective
Examine the prognostic implications of hyperglycemia and the importance of glycemic control in patients with and without DM during hospitalization for infectious diseases.
Methods:
Historical prospectively collected data of patients hospitalized between 2011 and 2013. Infection-related hospitalizations were classified according to site of infection. Median follow-up was 4.5 years. Outcome measures included in-hospital and end-of-follow-up mortality.
Setting
Historical prospectively collected data of patients hospitalized between January 2011 and December 2013.
Patients
Patients $\geq$18 years.
Main outcome
Length of stay, in-hospital and end-of-follow-up mortality.
Results
The cohort included 8051 patients (50% female, mean age $\pm$ s.d., 68$\pm$20 years) with a primary diagnosis of an infectious disease. Of these, 2363 patients (29%) had type 2 DM. The most common infectious sites included respiratory tract (n=3285), genitourinary tract (n=1804), skin and soft tissue (n=934) and gastrointestinal tract (n=571). There was no difference in admission rates of patients with and without DM according to the site of infection, except for skin and soft tissue infection which were more common among patients with DM (16% vs. 10%). In-hospital mortality risk was greater in patients with DM (aOR= 1.3, 95% CI =1.1–1.7). In the entire cohort, adjusted mortality risk (aHR, 95% CI) at the end-of-follow-up was greater among patients with DM (1.2, 1.1–1.4), with increased mortality risk following hospitalization for respiratory (1.1, 1.0–1.4) and skin and soft tissue infections (1.7, 1.3–2.3). In-hospital and end-of-follow-up mortality risk were highest among patients with and without DM with median glucose >180 mg/dl during hospitalization.
Conclusions
In patients hospitalized for infectious diseases, DM is associated with increased long-term mortality risk, specifically following hospitalization for respiratory and skin and soft tissue infections. Poor glycemic control in patients with and without DM during hospitalization is associated with increased long-term mortality.

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GP80

Self-reported low-energy fractures and associated risk factors in diabetic portuguese patients: a cross-sectional population-based study

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Introduction
Patients with diabetes have an increased risk of low-energy bone fractures (LEF). Traditional clinical risk factors and bone mineral densitometry underestimate LEF risk in diabetics. We aim to evaluate the frequency of LEF and associated risk factors in the diabetic Portuguese population.
Methods
National, cross-sectional and population-based study to describe the prevalence of self-reported LEF in diabetic subjects over 40 years-old. Estimates were computed as weighted proportions/means, considering sample design. Multivariate logistic regression models were used to assess predictors of LEF in the diabetic.
Results
In a national cohort of 10 661 people, 7675 subjects were over 40 years-old, of which 1173 were diabetic. Compared to nondiabetic, diabetic patients were older (mean age 66.0$\pm$11.49 years-old; 55.8% female), more overweight or obese (81.1% vs. 61.3%) and more frequently reported osteoporosis (20.4% vs. 15.4%) and falls in the previous 12 months (32.4% vs. 22.9%). Estimated prevalence of self-reported LEF was 16.2% (95% CI: 13.68–19.13, n=203) among the diabetic, compared to 13.3% (95% CI: 12.14–14.57, n=931) in nondiabetic (crude OR for the association between diabetes and LEF: 1.26, 95% CI: 1.01–1.58, P=0.045; in women, adjusted OR: 1.41, 95% CI: 1.05–1.89; in men, adjusted OR: 0.86, 95% CI: 0.57–1.31, P=0.481; P-value for the interaction between diabetes and gender: 0.008). In the diabetic patients, LEF were more frequent among women and increased with age; LEF of distal forearm were the most prevalent (13.9%, 95% CI: 9.26–20.28), followed by hip (5.2%, 95% CI: 2.54–10.49) and vertebral fractures (3.2%, 95% CI: 1.35–7.59). A third of the diabetic (95% CI: 25.80–35.0) reported at least one major LEF (hip, vertebral or distal forearm) and 70% (95% CI: 65.39–74.36) in other sites. Self-reported LEF were associated with female gender (adjusted OR 1.66, 95% CI: 1.07–2.56, P=0.023) and the occurrence of falls in the previous 12 months (adjusted OR 1.72, 95% CI: 1.12–2.63, P=0.013) in the diabetic subjects.
Conclusion
Diabetics reported more falls and had a higher prevalence of self-reported LEF than nondiabetic. Female gender and falls were associated with LEF in the diabetic. Our findings emphasize the need for fracture and falls preventive measures in diabetic patients.

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GP81

Impaired cortisol and growth hormone counterregulatory responses during severe hypoglycemia in type 2 diabetes mellitus

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Background
Cortisol and growth hormone elevations are critical counterregulatory responses to severe hypoglycemia. However, the proportion and clinical characteristics of type 2 diabetic patients who fail to show appropriate cortisol and/or growth hormone secretion in response to severe hypoglycemia have not been investigated.
Methods
We measured the plasma cortisol and growth hormone levels in type 2 diabetes with severe hypoglycemia (defined as blood glucose < 40 mg/dl with loss of consciousness) who visited the emergency department between 2006 and 2015.
Results
Of 187 hypoglycemic patients, 37 (19.8%) had impaired cortisol responses (<18 μg/dl) and 143 (76.5%) patients had impaired growth hormone responses (<5 ng/ml). There were 31 (16.6%) patients with impaired responses to both cortisol and growth hormone. The patients with impaired cortisol response, growth hormone response and both hormone response were significantly older (74.0, 76.0, 74.0 vs. 69.5 years) and had higher BMI (24.8, 23.7, 23.8 vs. 21.6 kg/m^2) compared with normal hormone response group. Individuals with impaired cortisol response group, impaired growth hormone response group and both hormone abnormal response group showed significantly higher admission rates (35.1%, 35.9%, 32.3% vs. 2.6%), lower growth hormone level (0.8, 0.8, 0.6 vs. 12.7 ng/ml), and lower adrenocorticotropic hormone (ACTH) level (20.0, 34.4, 19.5 vs 105.5 pg/ml) than individuals with normal hormone response group. Multivariate logistic regression analysis indicated that impaired cortisol response were significantly associated with growth hormone after adjusting for age, BMI, DM duration, and ACTH. Impaired growth hormone response were significantly associated with age, BMI, and ACTH after adjusting for eGFR.
Conclusion
A considerable number of type 2 diabetic patients have impaired cortisol and/or growth hormone responses to severe hypoglycemia. The type 2 diabetic patients likely to have abnormal GH response when they are older, have shorter DM duration, and have higher BMI.
Keywords: hypoglycemia, cortisol, growth hormone, type 2 diabetes mellitus, counterregulatory hormone response

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Diabetes Epidemiology

GP82

Maternal exposure to air pollutants and risk of gestational diabetes mellitus in Taiwan

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Objective
Mounting evidence has shown an increased risk of gestational diabetes mellitus (GDM) in association with elevated exposure to air pollution. However, limited

evidence is available concerning the effect of specific air pollutant(s) on GDM incidence.
Methods
We conducted this case-control study on 6717 mothers with GDM diagnosed in 2006–2013 and 6717 age- and year of delivery-matched controls to further address the risk of GDM in relation to specific air pollutant. Both cases and controls were selected from a cohort of 1-million beneficiaries of Taiwan's National Health Insurance program registered in 2005. Maternal exposures to mean daily air pollutant concentration, derived from 76 fixed air quality monitoring stations, within the 12-week period prior to pregnancy and during the 1st and 2nd trimesters were assessed by the spatial analyst method (i.e., ordinary kriging) with the ArcGIS.
Results
After controlling for potential confounders and other air pollutants, an increase in pre-pregnancy exposure of 1 inter-quartile range (IQR) for $PM_{2.5}$ and SO_2 was found to associate with a significantly elevated odds ratio (OR) of GDM at 1.10 (95% confidence interval (CI) 1.03–1.18 and 1.37 (95% CI 1.30–1.45), respectively. Exposures to $PM_{2.5}$ and SO_2 during the 1st and 2nd trimesters were also associated with significantly increased ORs, which were 1.09 (95% CI 1.02–1.17) and 1.07 (95% CI 1.01–1.14) for PM2.5, and 1.37 (95% CI 1.30–1.45) and 1.38 (95% CI 1.31–1.46) for SO_2.
Conclusions
It was concluded that higher pre- and post-pregnancy exposures to $PM_{2.5}$ and SO_2 for mothers were associated with a significantly but modestly elevated risk of GDM.

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GP83

Prevalence and predictors of gestational diabetes mellitus: a nationwide multicenter prospective study

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Aim
Gestational diabetes mellitus (GDM) is an important public health issue associated with significant short- and long-term morbidity both for mother and offspring. Prevalence rates of GDM show considerable variation among different countries and regions of the world. The primary aim of this study was to determine the nationwide prevalence and predictors of GDM in Turkey.
Materials and methods
We conducted a prospective nationwide screening among pregnant women. Between August 2016 and November 2017, a total of 2643 pregnant women from 51 centers in 12 different regions were enrolled. Two step screening method was used. All participants were screened with a 50-g glucose challenge test between 24 and 28 weeks of gestation. Those with values exceeding 140 mg/dl at 1 h underwent a 100-g oral glucose tolerance test on a different day. Carpenter Coustan criteria were used for the diagnosis of GDM. Clinical and biochemical data were obtained by electronic database software.
Results
The national prevalence of GDM was found to be 16.2% without a significant difference between urban and rural regions. Mean age and body mass index (BMI) of the study population were 29 ± 5 years and 25.1 ± 4.8 kg/m^2 respectively. Women with GDM were older (mean age 32 ± 5y vs. 28 ± 5y, $P<0.001$) and heavier (mean BMI 27.2 ± 5.1 kg/m^2 vs. 24.7 ± 4.7 kg/m^2, $P<0.001$) than their healthy counterparts. Prevalence of GDM tended to increase with age (6.9% in age <25y, 15.6% in 26–35y, and 32.7% in 36–45y, $P<0.001$). Maternal age, maternal BMI, history of previous GDM and family history of diabetes mellitus were independent predictors of developing GDM ($P<0.05$ for all). Low risk women (age <25y, BMI <25 kg/m^2, no family history of diabetes) comprised 10.7% of the whole population and the prevalence of GDM in these women was 4.5%.
Conclusion
The results of first nationwide study in Turkey indicate that GDM is very common affecting 1 out of 7 pregnancies in the country. Implementation of international guidelines on screening and management of this public health problem is required.

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GP84

Incretin hormones in pathogenesis of secondary hyperglycaemia in patients with Cushing's disease and acromegaly

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Aim of the study
To analyze the dynamics and levels of incretins and neuropeptides secretion in patients with CD and acromegaly and therefore to specify the pathogenesis of carbohydrate metabolism disturbances.
Methods
Forty-two patients with Cushing disease and acromegaly were included into the study. All patients were newly diagnosed with Cushing disease and acromegaly. Oral glucose tolerance test (OGTT), during which glucose, glucagon, glucagon like peptide 1 and 2 (GLP1, GLP2), gastric inhibitory peptide (GIP) and ghrelin were measured at 0, 30 and 120 min respectively was performed.
Results
The presence of prediabetes was higher in CD patients (40% vs 23% in acromegaly). Insulin resistance (assesed by HOMA-IR) was extremely high in both groups (11–13). In CD patients glucagon levels were significantly higher at all cut off points compared to controls (p 0 min $=0.001$, 30 min $=0.016$, 120 min $=0.025$). GIP secretion was lower in CD patients. Acromegaly group was characterized by inverse rhythm of GIP secretion, with no peak level at 30′ $P=0.324$. Basal GLP-1 level was significantly higher in CD patients ($P=0.047$). Both groups were characterized by unusual GLP-1 secretion with no peak levels at 30 min. No significant differences were found while analysing GIP and GLP-1 secretion in subgroups, divided regarding the stage of carbohydrate metabolism disorders. GLP-2 levels were significantly higher in CD patients (0 min $P<0.001$, 30 min $P=0.007$, 120 min $P<0.001$). Ghrelin levels were significantly higher in CD (0 min $P=0.013$ 30 min $P=0.002$ 120 min $P=0.003$) and acromegaly patients (0 min $P=0.048$ 30 min $P=0.023$ 120 min $P=0.015$) at all cut off points.
Conclusion
GIP and GLP-1 secretion in CD and acromegaly patients are characterized by an atypical rhythm with no peak levels which might mean that incretins are not playing the crucial role in carbohydrate disturbances that is seen in these patients. GLP-2 and ghrelin seem to influence and potentially regulate glucose homeostasis in CD and acromegaly patients.

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GP85

Association of glucagon-to-insulin ratio and nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus

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Objective
Although the importance of islet α-cell dysfunction in the pathogenesis of type 2 diabetes has been reappraised, data on whether increase or decrease of glucagon relative to insulin is related with glucose metabolism parameters or metabolic diseases such as nonalcoholic fatty liver disease(NAFLD) in clinical settings are

very limited. Therefore, we investigated the association between glucagon-to-insulin ratio(G/I ratio) and presence of NAFLD and metabolic parameters in T2DM.
Methods
This retrospective, cross-sectional study was performed with data obtained from 230 T2DM patients(mean age, duration of DM, and BMI:56 years, 8 years, and 25 kg/m^2, respectively). Participants were assessed for serum fasting and postprandial G/I ratio and divided into tertiles. NAFLD was defined as ultrasonographically detected fatty liver. Results: The patients in the lowest tertile of fasting G/I ratio had higher BMI, visceral and subcutaneous fat thickness(VFT, SFT), and HOMA-IR and shorter duration of DM. Fasting and postprandial G/I ratios were negatively correlated with BMI, VFT, SFT, fasting c-peptide, and HOMA-IR. In addition, postprandial G/I ratio was positively correlated with HbA1c levels, FBG, and HDL-C. Subjects with HbA1c $>8\%$ showed significantly higher mean G/I ratio than those with HbA1c $\leq 8\%$. Prevalence of NAFLD was significantly decreased across tertile of fasting and postprandial G/I ratio. Low G/I ratio was significantly associated with presence of NAFLD by both unadjusted analysis and after multivariate adjustment (OR, 95%[CI]:3.24[1.4–7.51], 2.59[1.03–6.55], respectively).
Conclusion
Our results suggest that the high glucagon relative to insulin may contribute to hyperglycemia, whereas low glucagon relative to insulin may contribute to NAFLD in T2DM.

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GP86

Heart rate variability is related to concomitant glucose fluctuation in longstanding type 1 diabetes

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The presence of type 1 diabetes (DM1) affects the heart rate variability (HRV). However, there are conflicting data on the impact of hyper- and hypoglycaemia on the parameters of cardiovascular autonomic regulation.
The aim
To investigate the possible association of glucose fluctuation with HRV in longstanding DM1.
Design and methods
We examined 49 patients with longstanding (>20 years) history of DM1 (without overt cardiovascular disease) and episodes of hyperglycaemia >160 mg/dl during 24-hour continuous glucose monitoring (CGM). In all patients, simultaneous 24-hour CGM and Holter electrocardiographic recording were performed. Time- and frequency HRV parameters were used as indicators of cardiovascular autonomic regulation. Patients were divided into two groups: with and without hypoglycaemia <50 mg/dl ($n=22$ and $n=27$, respectively).
Results
As compared to patients with hypoglycaemia, patients without hypoglycaemia had a significantly longer time of daily and early morning hyperglycemia >160 mg/dl ($P=0.001$ and $P=0.038$, respectively), as well as higher values of current and historical (mean values over the past 10 years) HbA1c levels ($P=0.019$ and $P=0.007$, respectively). Patients without hypoglycaemia had significantly lower values of time- and frequency domain HRV parameters. SDANN was positively related to duration of hypoglycemic episodes ($r=0.40$, $P=0.004$) and negatively correlated with total time of hyperglycemic episodes ($r=-0.41$, $P=0.003$). Furthermore, daily HF% was negatively linked to hyperglycaemia episodes ($r=-0.40$, $P=0.038$), but not to hypoglycaemia ($r=-0.08$, $P>0.05$). Presence of diurnal hypoglycaemia influenced the direction of HRV parasympathetic component response to episodes of daily and early morning hyperglycaemia. In patients without hypoglycemic episodes, hyperglycaemia was associated with decrease in daily HF% ($r=-0.40$, $P=0.038$), whereas in patients with hypoglycemic episodes, hyperglyceamia was linked to increase in HF% during both day and night ($r=0.45$, $P=0.034$ and $r=0.44$, $P=0.043$, respectively).
Conclusions
In patients with longstanding DM1, HRV is related to concomitant glucose fluctuation. Our findings suggest interactive effect of hypoglycaemia and hyperglycaemia on cardiovascular autonomic regulation.

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GP87

Differential expression of apoptotic and low grade inflammatory markers in Alzheimer's disease compared to diabetes mellitus type 1 and 2

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Objective
Neuroinflammation is a common primary or secondary mediator of the neurodegenerative process accompanying Alzheimer's disease (AD). Impaired brain insulin signaling, defining brain insulin resistance may represent a link between AD and type 2 diabetes mellitus (T2DM) while neuronal apoptosis may also be involved in the inflammatory process. Peripheral cytokine levels of IL-1β, IL-6, TNFα along with high sensitivity C-reactive protein (hsCRP) and apoptotic marker Fas ligand (FasL) were investigated in AD patients and they were compared with T1DM, T2DM.
Methods
We studied 93 patients: 41 with AD, 20 T1DM, 21 patients with T2DM and 11 healthy subjects. The number of cytokine-secreting peripheral blood mononuclear cells (nPBMCs) before and after mitogenic stimulation was determined for interleukin-1β (nIL-1β), interleukin-6 (nIL-6) and tumor necrosis factor-α (nTNFα) by the Enzyme-Linked-Immuno-spot assay. Serum levels of hsCRP and Fas ligand (FasL) were determined by ELISA.
Results
The studied subgroups did not differ in gender but differed in age. hsCRP had higher levels in AD (statistically significant difference only compared to T1DM, $P=0.02$) and lower in controls. The nPBMCs was higher in AD patients after stimulation than in basal conditions. This increase showed a statistically significant increase in nTNFα ($P<0.001$ versus T2DM, $P<0.001$ vs. T1DM, $P=0.005$ vs. control) and nIL-6 ($P=0.039$ vs. T2DM, $P<0.001$ vs. T1DM, $P=0.003$ vs. control) after stimulation with PMA, in all studied groups, but in basal conditions only nTNFα was higher in AD ($P=0.011$ versus control, $P=0.02$ versus T1DM). FasL concentrations in AD subgroup displayed statistically higher levels compared to all the other subgroups ($P<0.001$ versus T2DM, $P<0.001$ versus T1DM, $P<0.001$ versus control), while T2DM and T1DM subgroups had statistically lower levels compared to controls ($P<0.001$ and $P=0.035$, respectively) and T2DM had statistically lower levels compared to T1DM ($P<0.001$) ($P=0.08$). The nPBMCs was positively correlated with plasma levels of Fas-L after correction with age and this correlation was seen in AD subgroup only.
Conclusion
Low-grade systemic inflammation is higher in patients with AD compared to diabetic patients particularly after mitogenic stimulation. The Fas-FasL pathway, displaying the highest levels in AD and the lower in diabetes compared to control subjects, may have a role in this process as it is extrapolated by the positive correlation of FasL concentration and the magnitude of inflammatory response particularly in AD. Further investigation in the inflammatory-apoptotic pathway will shed light to any druggable pathway of ill-controllable AD.

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GP88

Gestational diabetes mellitus and continuous glucose monitoring system. A prospective study.

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Introduction
Gestational diabetes mellitus (GDM) is associated with an increase of maternal-fetal complications. Continuous glucose monitoring system (CGMS) detects postprandial hyperglycemia and hypoglycemia during 24h.
Methods
Women with GDM in gestational weeks 26–32 were allocated a CGMS (Ipro^{TM}2) after diagnosis in an observational prospective study. It was analysed: Mean glucose and standard deviation, area under the curve (AUC) with glucose >140 and <70. Percentage of glucose above or below the limit of normality before and after breakfast, lunch, dinner and night. (Target ranges: before meals 70–95, after meal 70–140 and night 70–120 (expressed: mg/dl)).
Results
$n=65$. Maternal age 33 ± 4.46 years (>35 years $=36.9\%$), family history of diabetes 65.3%, personal history of diabetes 21.3%, prepregnancy BMI 26.21 ± 4.74 kg/m^2 (>30 kg/m^2 $=23.1\%$), weigh gain 8.15 ± 5.47 kg, HbA1c 4.9%, insulin treatment 27.7%.
CGMS: Glucose before breakfast 87.63 ± 7.98, after breakfast 116.89 ± 19.57, before lunch 86.20 ± 10.08, after lunch 111.08 ± 18.19, before dinner 92.32 ± 11.79 and after dinner 109.22 ± 16.27 (mg/dl)
AUC $>140=0.62$ and $<70=0.64$.
Time glucose above or below range:

Table 1

Time (%)	Before breakfast (70–95)	After breakfast (70–140)	Before lunch (70–95)	After lunch (70–140)	Before dinner (70–95)	After dinner (70–140)	Night (70–120)
Above range	26.98%	19.35%	20.01%	11.30%	36.05%	7.41%	8.15%
In range	65.74%	79.94%	68.96%	85.67%	60.02%	89.27%	81.73%
Below range	7.28%	0.71%	11.03%	3.03%	3.03%	3.32%	10.12%

Conclusions
SMCG showed preprandial hyperglycemia, mainly before dinner. Few hypoglycemias were detected predominantly before lunch and night. Patients with GDM should have a narrow monitoring before and after every meal, especially before dinner, to prevent maternal-fetal complications.

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GP89

Depression screening in adults with diabetes

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Introduction
Elevated depressive symptoms and depressive disorders affect one in four patients with type 1 or type 2 diabetes (1). Thus, routine screening for depressive symptoms is indicated in this high-risk population. Current guidelines all recommend screening for depression in diabetic population(2). The Patient Health Questionnaire-9 (PHQ-9) is a valid screening tool for depression in individuals with diabetes (3). There is no specific data about the prevalence of depressive disorders diabetic population of Turkey. Therefore, we planned this study to investigate depressive disorder incidence in a small group of diabetic patient population.
Methods
The demographic and laboratory parameters including glycated hemoglobin (HbA1c), lipid levels and body-mass indexes (BMI) were measured and PHQ-9 questionnaire was applied to all the diabetic patients admitted our endocrinology department and accepted to participate in the study. We used a cut-off point of 10 and above as high risk for depression in PHQ-9 questionnaire.
Results
A total of 552 patients with diabetes (mean age 58.548 ± 12.13) were enrolled in the study. Based on the predefined PHQ-9 cut-off value, 87 (16%) participants had depressive disorders. The patients with depressive disorders had worse HbA1c (7.91 ± 2.05 vs. 8.52 ± 2.44 in depression negative and positive groups, respectively; $P=0.012$), BMI (31.54 ± 5.72 vs. 34.17 ± 7.96 in depression negative and positive groups, respectively; $P=0.005$). Although statistically unimportant, LDL-C, non-HDL-C and FBG levels were also higher in the depressive disorder positive group. Patients of whom HbA1c was above target (uncontrolled diabetes) had higher PHQ-9 scores and there was a positive correlation detected between PHQ-9 score and HbA1c values ($r=0.108$, $P=0.011$).
Conclusion
Depressive disorders prevalence is higher than expected in diabetic population. As recommended by guidelines every diabetic patient should be screened for depressive disorders periodically. PHQ-9 questionnaire is a practical and useful material for screening depressive disorders in diabetic patients.

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GP90

Nutritional composition of carbohydrate-rich gluten free products and glycemic index calculation of commercially available gluten free pasta

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Background
Celiac disease (CD) is an autoimmune enteropathy triggered by gluten ingestion in genetically susceptible individuals. Its prevalence is $\sim$7 times higher in type 1 diabetes (T1D) patients compared to the general population; in addition to adherence to a gluten free (GF) diet, these patients use carbohydrate counting to estimate their pre-meal insulin dosages. We aimed to (a) compare the nutritional composition between some GF and non GF carbohydrate-rich products available in the Greek market, and (b) calculate the GI of one commercially available, GF pasta.
Methods
We recorded the nutritional composition of 35 commercially available products (toasted bread, pasta and breakfast cereals). The in vivo GI was calculated for one specific GF pasta by comparing the plasma glycemic responses (area under the curve) in 10 healthy subjects (6 females, 4 males), after ingestion of (a) 50 g of glucose and (b) pasta containing 50 g of carbohydrate.
Results
Nutritional differences were identified between GF foods and their gluten counterparts (expressed as mean $\pm$ S.E.). Specifically, GF bread had lower energy and protein content per 100 g (1038 ± 7 VS 1123 ± 2 KJ and 4.0 ± 0.1 vs 9.0 ± 0.1 g respectively, $P<0.05$). GF pasta was higher in total carbohydrates but lower in simple carbohydrates and protein per 100 g (76.3 ± 2.1 VS 68.3 ± 1.5 g, 1.4 ± 0.3 vs 3.3 ± 0.1 g and 7.3 ± 0.7 vs 12.3 ± 0.2 g respectively, $P<0.05$). GF breakfast cereals' were higher in energy, saturated fat and simple carbohydrates, but lower in total carbohydrates, fiber and protein per 100 g (1906 vs 1580 ± 25 KJ, 4.2 vs 0.4 ± 0.2 g, 25.0 vs 9.4 ± 1.4 g, 70.8 vs 79.4 ± 4.6 g, 2.1 vs 5.3 ± 2.3 g and 6.4 vs 8.2 ± 1.2 g respectively, $P<0.05$). The *in vivo* calculated GI of the studied GF pasta (80% corn and 20% rice flour) was 32 ± 7 and its nutrient composition per 100 g was as follows: 78.5 g total carbohydrate, 0.5 g simple sugars, 1.2 g fiber, 6.5 g protein.
Conclusions
The present study revealed significant nutritional differences between GF and non GF products. The GI of the studied GF pasta was surprisingly low, probably due to the lower content in simple carbohydrates. T1D patients with CD should be aware of the high content of GF foods in total carbohydrates. All consumers should be advised to carefully read the food labels of GF products, as nutritional composition may vary considerably.

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GP91

Analysis of health-related quality of life in patients with type 2 diabetes mellitus: results of an epidemiological study FORSIGHT-T2DM

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Background
The aim of this study was to assess health-related quality of life (HRQoL) of patients living in cities and towns with different population in the Russian Federation (RF) using EQ-5D questionnaire, to calculate health utility index (QALY) and cost-utility ratio (CUR).
Methods
One of the goals of the multicenter, observational, epidemiologic study FORSIGHT-DM2 was to evaluate HRQoL using the EQ-5D Questionnaire. The study included more than 2000 patients with T2DM from 45 cities in the RF. We analysed the impact of different factors associated with the disease itself, specific features of its course, living conditions on the QoL. We performed a multivariable linear regression analysis to estimate the contribution of each independent variable to overall outcome.
Results
The proportion of patients with moderate or severe decrease in HRQoL status with respect to any parameter(s) was significantly higher among patients residing in small cities/towns with population less than 1 million inhabitants compared to patients residing in large cities (over 1 million inhabitants), including Moscow and Saint Petersburg ($P<0{,}001$). However, the self-reported health status was comparable in all groups. The assessment of HRQoL using a visual analogue scale (VAS) showed that mean score reflecting self-reported health status of patients with T2DM was 4.97 on a 10-point scale, $s=2.4$, (49.7 for on a 100-point VAS), after converting this measure of health status into QALY-weights the value was 0.503. The cost of one quality-adjusted life year (CUR) of T2DM patient in RF in 2014 was 209 417 rubles ($3722.4). It was estimated according to the QALY index calculations made in the FORSIGHT-DM2 study using the following equation: CUR = COI / QALY, COI being the total direct medical costs of treating DM2 and its complications and comorbidities amounting 105 337 rubles per patient ($ 2742). Diabetic foot syndrome, depression, diabetic osteoarthropathy, myocardial infarction in anamnesis, and age had the biggest negative impact on HRQoL. Our prognoses showed moderate correlations.
Conclusion
Patients with T2DM have lower HRQoL (49,7) compared to the general population of the Russian Federation in similar age groups (60,1 according to the ESSE-RF study). Health utility index and cost-utility ratio calculated within the study can be used as a criterion for the assessment of medical care quality for patients with T2DM in the RF.
Keywords: type 2 diabetes mellitus, pharmacoepidemiological study, European Quality of Life 5-Dimension Questionnaire (EQ-5D), health utility index, cost-utility ratio.
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GP92

Gestational Diabetes Mellitus is associated with increased risk of Non-Alcoholic Fatty Liver Disease: A population-based cohort study

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Background
Gestational diabetes mellitus (GDM) is associated with adverse perinatal outcomes, and increased risk of post-natal type 2 diabetes and cardiovascular disease. However, whether GDM increases the risk of developing incident Non-alcoholic Fatty Liver Disease (NAFLD) is unclear and has not been well examined in previous studies. This is important considering the significant health burden of NAFLD and the opportunity to interfere in high risk population in order to reduce the risk of developing end-stage liver disease.
Methods and results
We conducted a retrospective cohort study after extracting data from a large primary care database (The Health Improvement Network databse) in the United Kingdom. The cohort consisted of 9640 women with GDM diagnosis and 31 296 control women, matched for age, body mass index (BMI) and time of pregnancy. All study participants were free from NAFLD diagnosis at study entry. Mean (standard deviation) age of the whole cohort was 32.62 (S.D.: 5.34) years and BMI 28.62 (S.D.: 6.10) kg/m^2. There were 44 (0.46%) and 41 (0.13%) NAFLD incident diagnosis in the GDM and control population respectively over a median follow-up of 2.87 (IQR 1.16–5.81) years. Unadjusted incidence rate ratio (IRR) for NAFLD development was 3.28 (95% CI 2.14–5.02). After adjusting for age, Townsend (deprivation) quintile, smoking, BMI and Metformin usage; women with GDM remained at increased risk of developing NAFLD compared to women without GDM (IRR 2.95; 95%CI 1.91–4.55). Further adjustment for the diagnosis of polycystic ovarian syndrome, hypertension, hypothyroidism, and lipids lowering treatment did not change our findings (IRR 2.83; 95%CI 1.83–4.38).
Conclusions
Women diagnosed with GDM were at significantly increased risk of NAFLD development in their post-delivery life compared to women without GDM. Clinicians should have a low threshold to investigate women with history of GDM for the presence of NAFLD. Future studies need to examine whether lifestyle or pharmacological interventions could reduce the risk of developing NAFLD in women with history of GDM.
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Diabetes Therapy

GP93

Proinflammatory cytokines and endotoxemia level change in patients with type 2 diabetes and nonalcoholic fatty liver disease after hepatoprotective and probiotic therapy usage

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Association of type 2 diabetes, NAFLD, intestinal dysbiosis and endotoxemia is a trigger factor of cytokine cascade which manifest in proinflammatory state development, insulin resistance, hyperglycemia and dyslipidemia progression. The aim of this study is to reveal the effect of multiprobiotic Symbiter (symbiotic association of 14–24 strains of Bifidobacterium Lactobacillus, Propionibacterium, Lactococcus lactis, Streptococcus, Acetobacter aceti) and hepatoprotector Glutargin (arginine and glutamic acid salt) on proinflammatory cytokine levels and endotoxemia in patients with type 2 diabetes and NAFLD. Materials and methods. We observed 64 patients with type 2 diabetes and NAFLD who received oral hypoglycaemic agents, hepatoprotector Glutargin (0.75 g three times a day) together with multiprobiotic Symbiter (10 g twice daily) during 30 days. The control group consisted of 25 apparently healthy individuals. The concentration of the cytokines (IL 6, 8, TNF-α) in both blood serum and coprofiltrates and levels of antibodies to LPS in blood serum were determined by enzyme-linked immunosorbent assay (ELISA). The state of intestine microbiota was evaluated based on the results of bacteriological examination of faeces. Results and discussion. Before treatment patients with type 2 diabetes and NAFLD had significant increased blood proinflammatory cytokines concentrations indicating severe inflammatory and immunopathological reactions. We also revealed increased levels of IgG antibodies to LPS and proinflammatory cytokines in coprofiltrates which had strong correlation with dysbiotic disorders rate, reflecting the inductive role of Gram-negative flora endotoxin in inflammation progression in these patients. Conclusions. The use of Glutargin and multiprobiotic Symbiter complex reduced systemic inflammation by statistically significant decrease of serum proinflammatory cytokines and endotoxemia levels in patients with type 2 diabetes with NAFLD, which directly correlated with intestinal microbiota improvement. Due to this we consider that dysbiosis correction improve immunological status in this patients.
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GP94

Telemonitoring and Telemedicine for Type 2 Diabetes Care: Multi-center Randomized Controlled Trial

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The advent of Web-based patient management technologies, including Web-based messaging, video conferencing, remote monitoring of vital signs, and Web-based educational programs, has resulted in the recognition that telemedicine may benefit diabetic patients with limited access to healthcare providers and/or a high burden of disease. In this regard, 24-week prospective multi-center randomized controlled trial involved 338 adult patients with type 2 diabetes at four university hospitals in South Korea was performed to determine the effectiveness of the Smart Care service on glucose control based on telemedicine and telemonitoring compared with conventional treatment in patients with type 2 diabetes. The patients were randomly assigned to a control group (group A, $n=113$), a telemonitoring group (group B, $n=113$), or a telemedicine group (group C, $n=112$). Patients in the telemonitoring group visited the outpatient clinic regularly, accompanied by an additional telemonitoring service that included remote glucose monitoring with automated patient decision support by text. Remote glucose monitoring was identical in the telemedicine group, but assessment by outpatient visits was replaced by video conferencing with an endocrinologist. The adjusted net reductions in HbA1c concentration after 24 weeks were similar in the conventional, telemonitoring, and telemedicine groups ($-0.66\% \pm 1.03\%$ vs $-0.66\% \pm 1.09\%$ vs $-0.81\% \pm 1.05\%$; $P>0.05$ for each pairwise comparison). Fasting glucose concentrations were lower in the telemonitoring and telemedicine groups than in the conventional group. Rates of hypoglycemia were lower in the telemedicine group than in the other two groups, and compliance with medication was better in the telemonitoring and telemedicine than in the conventional group. No serious adverse events were associated with telemedicine. Telehealthcare was as effective as conventional care at improving glycemia in patients with type 2 diabetes without serious adverse effects.

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GP95

Randomized control study to compare security and efficacy of the new long acting analogues degludec and glargina U300 in people with type 1 Diabetes. Preliminary results of the Ineox study

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Background
There aren't published randomized studies comparing the clinical impact of degludec and Glragina U300 in the treatment of type 1 diabetes patients. (T1DP)
Objective
To compare efficacy and safety of the new long acting analogues Glargine U 300 and Degludec in 300 Type1 diabetes patients treated with basal/bolus treatment.(BBT)
Material and methods
Randomized control study 1.1 in 300 T1DP treated with BBT with glargineU100 or Detemir who change to GlargineU300 or Degludec at 1500 h during 24 weeks, with telematic visit (using Emminens platform) 6 weeks after the change of the treatment. The efficacy is mainly measured by change of HbA1c, secundary measures evaluated where variabilitu (SD,CV), BMI, insulin doses and quality of life (DQol). Safety measure being number of hypoglycemias (<54 mg/dl, <7 mg/dl and at night) and severe hypoglycemias during the whole 6 months period. We present the results of the first 150 recruited patients, age: 39.3 ± 11.7 years, sex (male 54%/female 46%), duration of the diabetes $19{,}43 \pm 11$ years, previously treated with Glargina U100 one or two doses (63%) or detemir two doses (37%)
Results
Globally there is a significative improvement at 24 weeks in HbA1c (7.8 ± 0.9 vs 7.6 ± 1; P 0.002) and also in porcentaje of hypoglycemias in glucometer download (13.6, $6 \pm 12\%$ vs $10{,}4 \pm 7{,}7$; P 0.005). We found no significant differences in all the studied variables except except for the lower insulin dose needed in the degludec group vs glargineU300 (IBasal 6 m: 27.4 ± 14 vs 34 ± 14,$P=0.009$; IBasal 6 m/kg: 0.36 ± 0.16, vs 0.46 ± 0.17,$P=0.001$; TDD(total daily dose)6 m/kg: 0.67 ± 0.25 vs 0.79 ± 0.27, $P=0.011$.
Conclusions
In T1DP the change of the treatment to the new long acting analogues degludec or Glargine U300 leads to an improvement in metabolic control in 24 weeks with less percentage of hypoglycemia and a a dose 22% inferior for degludec. We found no differences in metabolic (HbA1c, CV, BMI, Dqol) or safety variables(mild or severe hipoglucemias in 6 months) evaluadas. A larger number of patients and a longer period of follow up will help to corroborate those results.

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GP96

Long term results and determinants of outcomes in primary health care diabetes prevention. The DE-PLAN project

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Background
Real life implementation studies performed in different settings/populations proved that lifestyle interventions in prevention of DM2 can be effective. However, little is known about long term results of these translational studies and determinants of the outcomes.
Aim
The purpose of this study was to examine the maintenance of diabetes type 2 risk factor during 3 year follow-up and to examine determinants of long term outcomes.
Methods
Study participants ($n=263$), middle-aged, slightly obese with baseline increased DM2 risk (FINDRISC)>14), but no baseline diabetes were invited to receive 11 lifestyle counselling sessions, guided physical activity sessions and motivational support during 10-months. Examinations were performed baseline, after one/three years. Repeated measure analysis was used for comparison of the 3 measurements. Stepwise regression analysis was used to determine predictors of weight reduction maintenance.
Results
Mean weight decreased by 2.27 kg (S.D. $=5.25$) after 1 year ($P=<0.001$), the mean total weight loss at the end of the study was maintained by 1.14 kg (S.D. $=5.8$) (ns). 70% of participants showed weight loss during the intervention (mean weight loss 4.2 kg, S.D. $=5.1$), 37% maintained weight loss during the 3 year follow-up(mean weight loss 2.1 kg, S.D. $=2.3$) In repeated measures analysis significant changes were observed from baseline to year 1 and year 3 in: weight ($P=0.048$), BMI ($P=0.001$), total cholesterol ($P=0.013$), TG ($P=0.061$), fasting glucose level ($P=0.037$) and FINDRISC ($P=0.001$) parameters. The conversion rate to diabetes was 2% after 1 year and 7% after 3 years. In multivariate analysis baseline history of increased glucose (odds ratio (OR) $=3.7$; 95% confidence interval (CI) 1.0–13.6) and reduction of total fat in diet during follow-up (OR $=4.3$; 95% CI 1.5–12.2) were independent predictors of successful weight loss maintains during follow up.
Conclusions
Type 2 diabetes prevention in real life primary health care setting through lifestyle intervention delivered by trained nurses leads to long term modest weight reduction and decrease of diabetes risk. Further studies exploring predictors of success are needed to help health care providers to redesign interventions and improve long-term outcomes of real life interventions.

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GP97

Comparison of insulin degludec with Insulin glargin 300 units/ml in insulin-naive patients with type 2 diabetes mellitus

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Introduction:
Many type 2 diabetes patients continue to have poor glycaemic control and would benefit from insulin therapy. One of the risks that hinders insulin use is

hypoglycemia. Optimal insulin therapy should therefore minimize the risk of hypoglycemia while improving glycemic control. Newer insulin preparations degludec and glargin 300 units/ml show more even and prolonged pharmacokinetic profile, enabling an evenly distributed daytime glucose-lowering effect with high reproducibility of action.
Aims
The aim of the study was to compare efficacy and safety of the insulin degludec with glargin 300 units/ml in insulin-naive subjects with type 2 diabetes.
Patients and methods
In this 24-week, parallel-group, randomized, open-label, treat-to-target-trial, adults with type 2 diabetes with A1c >7% taking oral antidiabetic drugs (OADs) were randomized 1:1 to receive once daily degludec or glargin 300 units/ml, both with metformin. At randomisation, eligible participants discontinued all OADs (DPP-IV inhibitors, sulfonylureas, pioglitazone) with the exception of metformin. Degludec and glargin 300 units/ml were administered in the morning with breakfast. Insulin was titrated to achieve prebreakfast plasma glucose (PG) of 3.9–4.9 mmol/l. In order to control postprandial glycemia, DPP-IV inhibitors or repaglinide were introduced as needed.
Results
Study included 184 participants (mean age 68.5±8.5 years, mean duration of diabetes 12.0±4.7 years, mean BMI 27.2±2.6 kg/m^2, mean baseline A1c 9.5±1.4%) that were randomized (degludec 92, glargin 300 units/ml 92). Reduction in A1c with degludec was similar to that with glargin 300 units/ml (2.2% vs 2.3%, $P=0.7$). Overall rates of confirmed hypoglycemia (PG<3.9 mmol/l) were similar with degludec and glargine 300 units/ml (0.8 vs 0.9 episodes/patient-year). None of enrolled patients had severe or nocturnal hypoglycemia. End-of-trial mean daily insulin doses were 0.35 units/kg and 0.39 units/kg for degludec and glargine 300 units/ml, respectively, which was significant difference ($P=0.02$). Increase in body weight was observed: 1.8 kg and 1.5 kg for degludec and glargine 300 units/ml, respectively ($P=0.6$).
Conclusion
Despite the well-documented benefits of timely blood glucose control and the availability of consensus guidelines encouraging the earlier use of insulin replacement, a substantial delay remains with respect to the appropriate initiation of insulin treatment in routine clinical practice. BOT with both insulin degludec and glargine 300 units/ml are useful strategies that improve glycemic control in clinical practice without causing serious hypoglycemia.

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GP98

Adult-onset autoimmune diabetes: comparative analysis of classical and latent presentation

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Introduction
Adult-onset autoimmune diabetes (AID) has two different phenotypes: classic type 1 diabetes mellitus (T1DM), with insulin requirement just after diagnosis, and latent autoimmune diabetes in adults (LADA). According to the Immunology of Diabetes Society, LADA diagnostic criteria are: age of onset of 30 years or more, any islet autoantibody, absence of insulin requirement for at least 6 months. The purpose of this study is to characterize patients with AID followed on a tertiary centre, comparing classic T1DM and LADA.
Methods
We collected data from patients with diabetes and positive islet autoantibodies, with at least 30 years at diagnosis. We classified patients who started insulin in the first 6 months as T1DM and patients with no insulin requirements in the first 6 months as LADA. Data regarding presentation, autoantibodies, A1C and C-peptide at diagnosis, therapeutics and complications were analysed with SPSS.
Results
Ninety-two patients included, 46 with T1DM and 46 with LADA. In T1DM group, 50% female, in LADA 52.1%. The median age at diagnosis was 38 years in T1DM group and 42 years in LADA group. The median follow-up time after diabetes diagnosis was 8 years in T1DM and 11 years in LADA ($P=0.023$). The median time between diagnosis of diabetes and diagnosis of autoimmune cause was 0 months in T1DM and 60 months in LADA ($P<0.001$). The mean BMI at diagnosis was 23.52 kg/m^2 in T1DM and 26.07 kg/m^2 in LADA ($P=0.023$). The median number of positive autoantibodies was 2 in T1DM and 1 in LADA ($P=0.013$). There was no statistical difference between both groups in what concerns to title of GAD autoantibodies, A1C and C-peptide at diagnosis of autoimmune aetiology. The presence of symptoms at diagnosis was associated with T1DM group ($P<0.001$). There was no difference between both groups in A1C, lipid profile, glomerular filtration rate and BMI at the last evaluation. LADA group was associated with macroalbuminuria ($P=0.042$). The median daily insulin dose was 40U for T1DM and 33.5U for LADA. Patients in LADA group used more often non insulin antidiabetic drugs ($P=0.001$). There were no differences on other diabetes complications.
Conclusion
Patients with classic T1DM presented more often with symptoms at diagnosis, lower BMI and higher number of autoantibodies, which may be related to a more aggressive autoimmune process. Patients with LADA were associated with macroalbuminuria and were more often under non insulin antidiabetic drugs. The ideal treatment of LADA is yet to be identified.

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GP99

Optimal time for measuringglucose level to detect steroid induced hyperglycaemia

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Purpose
Steroid usage may cause hyperglycaemia in non-diabetic patients. We aimed to detect the onset of hyperglycaemia and the best time for glucose measuring over a short time span (1–5 days) in non-diabetic patients who commenced moderate or high dose steroid therapy.
Methods
Electronic data of patients, who were commenced moderate or high dose steroid therapy (15–60 mg prednisolone or equivalent dose methyl prednisolone) due to inflammatory rheumatologic diseases between January 2015 and December 2016, were retrospectively evaluated. The subjects who had confirmed diagnosis of DM were excluded. Seven point (morning fasting, pre-meal before breakfast, lunch, and dinner, and bedtime) capillary blood glucose measurements during the first 5 days of steroid therapy were evaluated. Results: 1750 premeal and postmeal glucose measurements were collected from 15 male (age 44±16 years) and 35 female (age 41±12) patients. Fasting blood glucose ≥126 mg/dl and random glucose ≥200 mg/dl were diagnosed with DM, while random glucose between 179 and 200 mg/dl was considered as hyperglycemia. 21 (%42) patients developed steroid induced overt hyperglycemia compatible with DM and 39 (% 78) developed hyperglycemia to a lesser extent. Mean fasting blood glucose was 88.04±9.9 mg/dl and hemoglobin A1c was 5.46±0.36% before steroid therapy. The highest glucose was detected postprandial on 3rd day of steroid therapy both in DM developers and non-DM developer hyperglycaemia group (234±29 vs 180±18 mg/dl, $P<0.0001$). DM developers and non-DM developers did not show significant difference in terms of steroid dose, age, BMI, baseline hemoglobin A1c, previous steroid therapy history, underlying rheumatologic disorder, or family history of DM.
Conclusions
Fasting blood glucose may be normal and postprandial hyperglycaemia may be present in endogenous steroid excess due to Cushing' syndrome and exogenous steroid usage. It is not recommended to monitor glucose levels during low dose steroid therapy, while moderate or high dose steroid therapy demands follow-up. It is especially important in outpatients to detect the best time for measurement. We showed that the highest values were postprandial levels on 3rd day of therapy in patients taking moderate-high dose of steroid. As a result we recommend measuring postprandial instead of fasting glucose levels during first 3 days of moderate-high dose of steroid therapy.

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GP100

Effect of aerobic exercise training on serum malondialdehyde level and quality of life in type 2 diabetes

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We planned to research the effect of the regular exercise of type 2 diabetes mellitus (DM) patients on metabolic control, malondialdehyde (MDA) as the oxidative stress marker and on the quality of life. The study has been carried out 64 patients diagnosed with Type 2 DM for at least 6 months, without any microvascular/macrovascular complication for diabetes, using oral anti-diabetic agent with a HbA1c value of less than 9%. The 31 patients were asked to carry out aerobic exercise under supervision based on the American Diabetes Association recommendations, in 3 non-successive days for 150 min a week in 12 weeks. Both groups were given a diet. Systolic and diastolic blood pressure (SBP, DBP), body mass index (BMI), waist/hip measurements were made in the beginning and in the end of the study. Venous blood samples were taken for HbA1c, insulin, lipid panel and MDA analysis and Short Form Health Survey (SF-36) quality life questionnaire form was applied. All parameters within and between the groups were compared as a result of the 3-month-period. In the exercise group, there have been statistically significant reductions in the BMI ($P=0.017$) and MDA ($P=0.046$) levels in the measurement of SBP ($P=0.027$), DBP ($P=0.042$), waist circumference ($P=0.01$). There has been an increase in the tendency of statistical significance in the mental health sub score ($P=0.06$) of the SF-36 questionnaire form as well as increases in other sub scores including physical and mental scoring. In the control group, there has been a statistically significant decrease in the general health scores ($P=0.006$). In the end of the study, there has been a statistical increase in favour of the exercise group compared with the control group in the sub scores of general health ($P=0.02$) and mental health ($P=0.03$) as compared with the initial values. Twelve weeks aerobic exercise program for the type 2 diabetic patients has been effective in reducing the MDA level, which is the oxidative stress indicator. In the exercise group, there has not been any significant change in the metabolic parameters after the twelve weeks long aerobic exercise, however, there has been increases in favour of the general health and mental health scores of the quality of life when compared to the control group. In order to observe improvements in metabolic parameters, there is need for studies to be conducted with more patients for longer periods and including combined exercise programs.

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GP101

A healthier fat intake is associated with absence of diabetic retinopathy in patients with type 1 diabetes

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Background
Medical nutrition therapy is an important part of the management of type 1 diabetes mellitus (T1DM). Proper adherence to a healthy diet may have a favorable impact on diabetic complications. Our aim was to assess differences in food and nutrient intake of type 1 diabetic patients with and without diabetic retinopathy (DR).
Subjects and methods
This was a two-center, cross-sectional study in patients diagnosed with T1DM with and without DR. Subjects were recruited through the DR screening program of the Departments of Ophthalmology. A validated food frequency questionnaire was administered. Clinical variables were collected. The analysis of data included comparison between groups and multivariable models.
Results
A sample of 103 T1DM with DR and 140 T1DM without DR were recruited. Subjects with DR showed a lower intake of total fat ($P=0.036$) than their non-DR counterparts. DR was associated with increasing age ($P=0.004$), hypertension ($P<0.001$) and diabetes duration ($P<0.001$), and there was a negative association with high educational level ($P=0.018$). The multivariable adjusted analysis showed that the intake of complex carbohydrates was positively related to the presence of DR ($P=0.018$). In contrast, the intakes of total fat ($P=0.004$), monounsaturated fatty acids (MUFA) ($P=0.005$), oleic acid ($P=0.005$), α-linolenic acid ($P=0.041$) and vitamin E ($P=0.004$) were associated with the absence of DR.
Conclusions
The intake of total MUFA, oleic acid, α-linolenic acid and vitamin E is associated with a lower frequency of DR in patients with T1DM. These results suggest a potential protective effect of these lipid components for DR.

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GP102

Type 2 diabetes remission one year after bariatric surgery – a comparison between vertical sleeve gastrectomy and gastric bypass

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Background
Gastric Bypass surgery (Bypass) is recognized as the ultimate metabolic surgery. The success in type 2 Diabetes (DM2) remission documented in patients submitted to Vertical Sleeve Gastrectomy (Sleeve) made questionable the hypothesis that this restrictive surgery has beneficial metabolic effects.
Main goal
Comparing the Bypass and Sleeve's efficacy in DM2 remission.
Methods
Retrospective study of 112 diabetic patients submitted to bariatric surgery in Hospital de Braga from January of 2011 to December of 2016. For each patient, the data was collected from the clinical process and Body Mass Index (BMI), fasting glucose and insulin, glycated haemoglobin (HbA1c) and diabetic therapy were compared at 0 and 12 months. The criteria used for the definition of DM2 remission was the American Diabetes Association's. The statistical analysis was made through the SPSSvs22 program, with T-test for correlated and independent samples (significance level of 0.05).
Results
From the 112 patients included in the study, 63 performed Sleeve, with 74.6% female ($n=47$) with a medium age of 47.63 ± 11.7 years. The remaining 49 performed Bypass, with 79.6% female ($n=39$) and a medium age of 50.29 ± 10.0 years. Twelve months later, with Sleeve, patients presented a medium reduction of the BMI of -13.40 ± 4.7 kg/m^2 and with Bypass of -13.55 ± 5.3 kg/m^2, statistically significant. Nevertheless there were no differences statistically significant in the magnitude of reduction of BMI between both surgeries. Concerning fasting glucose, Sleeve allowed a medium reduction of -29.69 ± 31.8 mg/dl and Bypass of -47.23 ± 53.0 mg/dl, without differences in the magnitude of reduction between both surgeries ($P=0.076$). Fasting insulin after Sleeve decreased a medium of -10.75 ± 10.5 uUI/ml and after Bypass -20.68 ± 12.9 uUI/ml. Regarding HbA1c, with Sleeve, patients obtained differences of -0.85 ± 0.9% and with Bypass a medium of -1.50$\pm$1.6%. Bypass showed a more significant reduction in insulinemia ($P=0.001$) and HbA1c ($P=0.039$). One year after Sleeve, 42.9% of the patients kept the DM2 therapy ($n=27$). Of the patients submitted to Bypass, 46,9% didn't suspend the medication ($n=23$). Twenty patients went on DM2 remission after Sleeve ($n=31.7$%) and 17 after Bypass (34.7%).
Conclusion
Both surgeries allowed DM2 remission after one year. Despite Sleeve and Bypass had equivalent reductions of BMI and fasting glucose, Bypass allowed a more significant reduction in fasting insulin and HbA1c values, independently of weight loss.

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GP103

Glycemic control and outcomes of patients admitted in the acute stroke unit

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Introduction
Post-stroke hyperglycemia affects two-thirds of the patients during acute ischaemic stroke and it is associated with poorer outcomes. The aim of this study was to analyze the differences between the diabetic and non- diabetic patients that underwent an acute stroke.
Methods
Retrospective descriptive study of patients admitted to the Acute Stroke Unit from January to June 2017, including blood parameters, glycemic treatment and 3 months outcomes.
Results
From January to June 2017, 126 patients were admitted to the Acute Stroke Unit. 28,6% of them with a previous diagnosis of diabetes. More than half of the patients were men and the mean age was 73.2 (s.d. 9.0) in diabetics and 71.9 (s.d. 12.8) in non-diabetics. 17% ($n=6$) of the diabetic patients needed thrombolysis versus 11%($n=10$) of non diabetics. Mean HbA1C was 7.4% (s.d. 1.4) in diabetics against 5.6% (s.d. 0.39) in non-diabetics. Mean glucose level in diabetics at admission was 166.0 mg/dl (s.d. 67.6) and in the first 72 hours 159.2 mg/dl (s.d. 51.5) starting treatment with an average of 185.0 mg/dl (s.d. 53.6). The most common treatment used was IV insulin 41.7% ($n=15$), sliding-scale SC insulin 19.4% ($n=7$), sliding-scale with basal SC insulin 14% ($n=5$) and only one patient received metformin on the acute treatment. 22.2% ($n=8$) of the diabetic patients had no treatment during admission. In non-diabetic patients, the mean glucose level at admission was 108.0 mg/dl (s.d. 19.8) and in the first 72 hours 104.4 mg/dl (s.d. 16.0). Only one of them developed stress hyperglycemia and was treated with sliding-scale SC insulin. Regarding outcomes, 41.7% of diabetics had a total recovery, 50% developed sequels and 8.3% died versus 51.1%, 45.6%, 3.3% in non-diabetics. 16.7% of the diabetics were readmitted in less than 3 months versus 12% of the non-diabetics, not statistically significant. The outcomes were related with the glucose level when treatment was started, 173.5 mg/dl (s.d. 57.4) in those with a total recovery, 189.4 mg/dl (s.d. 50.9) the ones that developed sequels and 202.0 (s.d. 32.6) in those that died during the admission, although the differences were not statistically significant.
Conclusions
Diabetic patients seemed to have poorer outcomes after a stroke. The poorest outcomes seemed to be related to the highest glucose level when treatment was started, although our sample was not large enough to detect significant differences. Almost 20% of diabetics received sliding-scale SC insulin although studies had shown is not an appropriate treatment.

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GP104

Validation of Friedewald formula for estimatinglow-density lipoprotein cholesterol in Korea: the Korea National Health and Nutrition Examination Survey, 2009–2011

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Objectives
The aim of this study is to compare Friedewaldestimated and directly measured lowdensity lipoprotein cholesterol (LDLC) values and assess the concordance in guideline risk classification between the two methods.
Methods
The data were derived from the 2009 to 2011 Korea National Health and Nutrition Survey (KNHANES). Analysis was done for 6454 subjects with lipid panels – total cholesterol (TC), directly measured LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG).
Results
For subjects with TG <400 mg/dl, overall concordance in guideline risk classification was 79.1%. The Friedewald formula tended to underestimate LDL-C more at higher TG or lower HDL-C levels. Especially, the percent of subjects who were misclassified into a lower risk category was 31% when TG were 200–299 mg/dl; and 45.6% when TG were 300–399 mg/dl. A greater under-estimation of LDL-C occurred at higher TG and lower Friedewaldestimated LDL-C levels. Of subjects with a Friedewaldestimated LDL-C <70 mg/dl, 55.4% had a directly measured LDL-C ≥ 70 mg/dl when TG were 200–399 mg/dl.
Conclusions
The Friedewald equation tends to underestimate LDL-C in highrisk subjects such as hypertriglyceridemia and hypo-HDLcholsterolemia. For these individuals accurate assessment of LDL-C is crucial, and therefore additional evaluation is warranted.

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Diabetes Translational

GP105

Acute insulin-induced hypoglycemia decreases systemic fibrinolytic balance in patients with type 1 diabetes

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Background and aims
Hypoglycemia can be a risk factor for adverse cardiovascular and cerebrovascular events. However, changes in platelets and coagulation hemostasis during hypoglycemia have not been extensively studied. During hypoglycemia, a wide spectrum of physiologic responses are activated that could have potential vascular biological effects. To date, the role played by catecholamines, the sympathetic nervous system, and neuroendocrine hormones on activating adhesion molecules and influencing fibrinolytic balance is incompletely understood. The aim of this study was to assess the impact of insulin-induced hypoglycemia on the platelet activity, and fibrinolysis in patients with type 1 diabetes.
Research design and methods
We studied 15 patients with type 1 diabetes (9 male and 6 female, age 24.4 ± 5.6, A1C $9.07\pm2.3\%$) without microvascular complications during hyperinsulinemic (1 mU/kg per min) hypoglycemic clamp protocol. Induced platelet aggregation in whole blood using thrombin receptor activating peptide 6 (tRaP-6), collagen, arachidonic acid, adenosine-diphosphate, ristomycin was measured during hypoglycemia (plasma glucose(pg) 2.3 ± 0.1 mmol/l), euglycaemia (pg 4.4 ± 0.4 mmol/l), hyperglycemia (pg ≥ 12 mmol/l) and recovery phase by multiple electrode platelet aggregometry (Multiplate). Plasminogen activator inhibitor (PAI-1), tissue plasminogen activator (tPA) was determined by ELISA. Statistical analysis was performed with SPSS 22,0 for Windows, $P<0.05$.
Results
Platelets aggregation induced collagen ($P=0.001$), thrombin ($P=0.003$), adenosine- diphosphate ($P=0.016$), arachidonic acid ($P=0.05$) was significantly increased during 20-min of hypoglycemia compared with euglycemia. Plasma PAI-1 activity were significantly different during hypoglycemia as compared with euglycemia ($P=0.001$) and as compared with recovery phase ($P=0.018$). Plasma concentrations of tPA did not alter during either hypoglycemic clamp in individuals with type 1 diabetes.
Conclusions
The present study confirmed that platelet activation is promoted by hypoglycemia and that hypoglycemia decreases systemic fibrinolytic balance by increasing PAI-1 activity while maintaining tPA values. Thus, at least two separate mechanisms for increasing thrombosis are activated by hypoglycemia in individuals with type 1 diabetes.

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GP106

Transcranial duplexsonography in patients with type 1 diabetes and diabetic nephropathy

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Background and aims
Cerebrovascular reactivity (CVR) impairment was reported as a marker of cerebral microangiopathy in long-term type 1 diabetes (DM1). Indices of cerebral

blood flow might serve as an indicator of early microangiopathic complications. The aim of this study was to evaluate CVR in patients with DM1 and diabetic nephropathy. Research design and methods: Study has been reviewed by the Local Ethics Committee. The study has been performed in accordance with ethical standards laid down in the Helsinki Declaration. Peak systolic blood flow velocity (S) in the middle cerebral artery (MCA) before (S1) and after (S2) compression of the ipsilateral common carotid artery (CCA) and the index of vasomotor reactivity (VMRr = (S2–S1) × 100/S1) were measured with transcranial duplex sonography in 41 patients (age 28.9 ± 6.2 years, duration of DM1 15 ± 4 years, HbA_1c 8.9 ± 1,8%) with DM1, without history of cerebrovascular events, and 22 healthy control subjects (age 26.3 ± 4.2 years). The study included patients with normoalbuminuria AER in the morning urine < 20 mg/l ($n = 22$); microalbuminuria AER < 199 mg/l ($n = 12$); macroalbuminuria AER ≥ 200 mg/l ($n = 7$). A decrease of glomerular filtration rate (GFR) of 45–59 ml/min per 1.73 m^2 was noted in 6 patients, in 35 patients with GFR ≥ 60 ml/min per 1.73 m^2. Statistical analysis was performed with SPSS 22,0 for Windows, $P < 0.05$.

Results

There was statistically significant decrease of VMRr in patients with DM1 compared with control group ($P = 0.01$) (*U*-test). S in the MCA before compression of the CCA was not different in the study groups. S had statistically significant decrease after compression in the group of patients with GFR 45–59 ml/min per 1.73 m^2 compared with the group of patients with GFR ≥ 60 ml/min per 1.73 m^2 ($P = 0.008$) (*U*-test). S after compression was higher in patients with macroalbuminuria compared with normoalbuminuria ($P = 0.019$)(*P*-test). There was not statistically significant difference depending on HbA_1c level, duration of DM1, age, hypertension, smoking, presence and severity of diabetic retinopathy.

Conclusion

The CVR was reduced in patients with DM1. In patients with diabetic nephropathy (macroalbuminuria or GFR < 60 ml/min per 1.73 m^2), the ability of the MCA to change diameter under the influence of mechanical factor is reduced that leads to a disruption in the ability of the cerebral circulation to compensate a hemodynamic deficit. Diabetic nephropathy can indicate the severity of cerebral microangiopathy in patients with DM1.

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GP107

Cumulative effect of glucose regulation in Calbindin-D9k knockout mice

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Cellular Ca2+ signals have been proposed to activate signal for hormone secretion. In pancreatic β cell which produce insulin, Ca2+ signals have been known contributing insulin secretion. Prior to conduct this study, we confirmed calbindin-D9k (CaBP-9k) which responsible for regulation of the distribution offree calcium in the cytoplasm. Hypoxic condition induces endoplasmic reticulum(ER) stress, increase both insulin signaling and insulin resistance. Byexposing hypoxia, CaBP-9k KO mice showed more increased level of ER stressmarker protein than wild type mice. To examine the cumulative effacement of CaBP-9k molecule ablation, we did examined the glucose tolerant test for 6, 12, 18 24 months old mice. After 6 month, CaBP-9k KO mice showed delayedregulation of serum glucose after glucose administration. Serum insulin of CaBP-9k KO mice were decreased compare to wildtype mice. In addition, theinsulin transcription factors of CaBP-9k KO mice (Mafa, Pdx, NeuroD1) have been downregulated. It demonstrated that CaBP-9k is not only the part of the insulin-secreting calcium signaling but also insulin working mechanism which could link to pathology for exacerbating type 1diabetes to type 2 diabetes.

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GP108

The effect of GLP-1 agonist treatment on serum betatrophin levels and comparison with insülin treatment in type 2 diabetes mellitus patients

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Objective

Insulin insufficiency which is the result of deficiency of β-cells is the common feature for all types of diabetes. Therefore protection of functional β-cell mass is the keystone of diabetes treatment. Betatrophin, a newly determined hormone, has been identified as a potent stimulator that increases the production and expansion of β-cells in mice. However, very little is known about the physiological role of betatrophin in human.Chronic treatment of rodents with GLP-1 agonists can result in an increase in β-cell mass due to increases in β-cell proliferation, neogenesis and decreases in β-cell apoptosis.The aim of this study is to show the effect of GLP-1 agonist treatment on betatrophin levels and comparison with insülin treatment in type 2 diabetic (T2DM) patients. This is the first human study in the literature with relation between betatrophin and GLP-1 treatment.

Methods

This prospective study included 27 patients with uncontrolled T2DM which were treated with metformin and sulfonylurea. 17 patients were enrolled in GLP-1 group and 10 patients were insulin group. Fasting betatrophin levels were evaluated before and at the 6.th month of treatment.

Results

Demographical features and BMI of two groups were similar. Betatrophin levels decreased in both groups after 6 months of treatment. But no statistical difference is observed between compared groups ($P = 0.473$). The reduction in betatrophin levels were only significant in insülin treated group ($P = 0.017$). There were no significant relation between betatrophin and c-peptid levels ($P = 0.903$). Also betatrophin levels were not correlated with age, sex, duration of diabetes, variables of glucose and lipid profiles.

Conclusion

Betatrophin levels were decreased significantly in insulin group but not in GLP-1 group. Incretin based treatments are known to increase β-cell mass and betarophin is a potent stimulator of β-cells. As betatrophin levels were still high in subjects on GLP-1 treatment it can be postulated that betatrophin would be a pathway on β-cell increment during GLP-1 treatment in long-term. However, in order to obtain more significant results further studies with higher number of patients and long-term follow-up is needed.

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GP109

High glucose stimulates mineralocorticoid receptor activity of retinal Müller glia cell

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Activation of mineralocorticoid receptor (MR) is shown in diabetic pathophysiology. We have investigated the activation mechanism of MR protein in diabetic nephropathy and clarified one of the mechanisms of activation of MR protein by hyperglycemia. On the other hand, MR is abundantly expressed in the retina. Retinal Müller glial cells are known to be involved in the control of retina hydration and homeostasis of potassium through MR and it is reported that treatment of MR antagonist is effective in central serous chorioretinopathy that causes edema between retina and choroid. Therefore, it is suggested that MR may be involved in edematous diseases of the retina. In diabetic macular edema, the role of VEGF has been demonstrated in recent studies, but a detailed mechanism of edema remains largely unknown. In this study, we confirmed the MR pathway in human retinal Müller glial cells and observed the response by hyperglycemia stimulation. We examined the MR pathway with MIO-M1 cell line which is a naturally immortalized retinal Müller glial cell line derived from human retina. We confirmed that MR proteins and mRNA are expressed in MIO-M1 cells by Western blotting and real time RT-PCR. Furthermore, we confirmed SGK1 and αENaC which were a target gene of the MR. We treated MIO-M1 cells with aldosterone. Aldosterone induces a significant up-regulation of MR, αENaC and SGK1 mRNA expression in MIO-M1 cells. For the examination of the diabetic retina, we treated MIO-M1 cells with high glucose (HG) condition and examined the effect of HG on MR activities. As a control, normal glucose (NG) was treated. HG treatment increased the 2.2 times MR protein levels in MIO-M1 cells ($P < 0.01$). On the other hand, MR mRNA did not change. Regarding MR target genes, SGK1 mRNA was significantly increased in HG compared to NG (6 h: $P < 0.001$, 12 h $P < 0.01$) but αENaC did not change. In Müller cells of the retina, hyperglycemia stimulates MR signal activity and may be associated with aggravation of edema. In this study, MR protein was increased, but MR mRNA was not increased in hyperglycemic condition. Regarding the mechanism of increase in MR protein, it was suggested that stimulation of hyperglycemia may induce activation of the translational factor and suppression of MR protein degradation.

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GP110

Knock-down of class 2a histone deacetylases (HDACs) in hepatocytes of healthy mice does not affect gluconeogenesis but is associated with increased hematopoiesis

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Class 2a HDACs (i.e. HDAC 4, 5, 7 and 9) are involved in the regulation of gluconeogenesis and accordingly, their inhibition has been shown to result in lower blood glucose and improved pyruvate tolerance in diabetic mice. However, pan-inhibition of HDACs is not a viable approach for chronic treatment of type 2 diabetes (T2D) due to induction of severe side effects in various tissues. We now have investigated *in vitro* and *in vivo* efficacy and safety of a liver-selective HDAC knock-down via single or combinatorial siRNAs for HDAC 4, 5 or 7. In mouse and human hepatocytes, siRNAs directed against HDAC4, 5 or 7, as well as the combination of all three siRNAS, led to a selective knock-down of the respective HDAC mRNA(s) by about 80-90%. In parallel, genes involved in the regulation of gluconeogenesis, namely G6PC and PCK1, were significantly down-regulated by 70–80% in primary hepatocytes. Those siRNAs were used either alone or in dual or triple combinations (0.75 mg/kg) to treat healthy 9-week old C57BL/6J mice with five intravenous injections for 25 days, as control served either PBS, or a non-silencing control siRNA. After the 4th injection, data from an intraperitoneal pyruvate tolerance test (PTT) in 16 h fasted mice showed no significant differences in glucose excursion. Furthermore, no significant effects on fasting blood glucose and plasma insulin were observed between treatment groups. Quantitative real-time PCR demonstrated a significant hepatic down-regulation of the respective HDACs mRNA by 60–80%. However, no reduction of the gluconeogenic genes PCK1 and G6PC was detected in livers of mice. During microscopic examination of key tissues, adverse findings were increased hematopoiesis in spleens of 15/49 mice and chronic purulent pyelonephritis in individual animals (5/49) treated with the different targeting siRNAs. In contrast, spleens and kidneys of mice treated with the non-silencing control siRNA displayed no adverse findings. While the pyelonephritis may indicate an ascending bacterial infection after immunosuppression, the pathomechanism of increased hematopoiesis remains unclear. In summary, although active in cell culture, liver-targeted siRNA knockdown of class 2a HDACs did not translate in an inhibition of genes regulating gluconeogenesis in vivo. Lack of glucose lowering properties in vivo as well as the detection of increased hematopoiesis hamper a clear path forward for development of this approach for treatment of T2D.

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GP111

Olfactory receptor OR51E1 mediates GLP-1 secretion in enteroendocrine L cells

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Few studies have investigated the intracellular signaling pathways mediating the effects of glucagon-like peptide-1 (GLP-1) secretagogues in enteroendocrine L cells. Specific receptors, channels, and intracellular signaling proteins expressed by the L cells have only begun to be characterized. The present study aimed to investigate the role of the olfactory receptor (OR) OR51E1 in GLP-1 secretion. We verified the expression of olfactory marker protein (OMP), an indicator of OR-mediated events in non-olfactory systems, in human intestinal L cells. Furthermore, we analyzed OMP and OR51E1 expression in the human L cell line NCI-H716. To investigate whether odorant-activated OR signaling stimulates GLP-1 secretion, we employed nonanoic acid, a known OR51E1 ligand. Treatment with 100 μM nonanoic acid increased GLP-1 secretion by 2.09 ± 0.39 folds; however, this effect was ameliorated on *OR51E1* knockdown. Oral administration of nonanoic acid to rats resulted in a 2.89 ± 0.53-fold increase in circulating GLP-1 levels and reductions in blood glucose levels compared to those in the control group. Our findings suggest that nonanoic acid stimulates GLP-1 secretion via OR51E1 signaling in intestinal L cells, thereby indicating an essential role of OR-mediated events and the corresponding odorants in GLP-1 secretion.

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GP112

Study on antioxidant and hypoglycemic effects of natural polyphenols in the experimental diabetes model

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According to the findings from the recent studies, the oxidative stress can be a cause for type 2 diabetes mellitus onset. In that context, the development of drugs with antioxidant effect to be used for prevention and treatment of the disease is of vital importance. The work was initiated to study the oxidative stress in the experimental diabetes and methods of its correction by means of natural antioxidants. In our study we used polyphenols isolated from the seeds of common grape vine (*Vitis vinifera*) and the leaves of upland cotton (*Gossypium hirsutum*), as well as the safflower (*Carthamus tinctorius L.)* extract. The antioxidant activity of the agents was assessed *in vitro* by ability to inhibit the adrenalin autoxidation; in tissue homogenates it was assessed by measuring concentrations of oxidates and activity of enzymes in the antioxidant system. Intensity of antioxidant activity of the agents above was compared to the one observed in quercetin, a flavonoid used as a reference product. All the agents under study demonstrated antioxidant effects close to the one produced by quercetin. To assess the hypoglycemic effect of the agents, in white outbred rats weighing 230–280 g type 2 diabetes mellitus was induced by three-fold intraperitoneal administration of diabetogenic dose of alloxan. When blood serum glucose was higher than 9–11 mmol/l the agents under study were administered to the experimental animals intragastrically in the doses providing optimal concentrations. Polyphenols isolated from *Vitis vinifera* and *Gossypium hirsutum* as well as *Carthamus tinctorius L.* extract were found to reduce the blood serum glucose in the diabetic animals by 50.0, 45.9% and 41.7%, respectively. Of note, gliclazide (Servier, France), the second generation sulfonylurea derivative, used as an oral hypoglycemic agent, reduced the parameter by 45.9%. The agents under study demonstrated both antioxidant and hypoglycemic effect. The hypoglycemic effect of agents under study observed in the type 2 experimental model could be associated with the antioxidant effect they produced.

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GP113

Diazoxide pretreatment improves pancreatic islet survival *in vitro* and functionality *in vivo*

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The efficacy of human islet transplantation is reduced by loss of islets directly after transplantation. Ischemia is likely to be an important contributing factor to the observed islet loss. Diazoxide inhibits insulin secretion by beta cells and has been shown to exhibit anti-apoptotic and anti-ischemic effects. We hypothesized that preincubation of human islets with diazoxide leads to improved islet survival and graft function.

Methods

Isolated human pancreatic islets were incubated in CMRL1066 culture medium with or without diazoxide 260 μmol/l for 72 h. After incubation, a sample was taken to assess islet viability (FDA-PI staining) and function (glucose stimulated insulin secretion, GSIS). Islets (3000 IEQ) were transplanted under the kidney capsule of NOD-SCID mice which had been rendered diabetic by intraperitoneal injection with streptozotocin. Fourteen days after islet transplantation, the mice underwent an intraperitoneal glucose tolerance test (IPGTT) to assess endogenous human C-peptide production and glucose tolerance.

Results

83.2 ± 4.0% of islets pretreated with diazoxide were viable compared to 76.0 ± 4.2% of islet incubated without diazoxide ($P < 0.001$). Islet function *in vitro* did

not differ (GSIS ratio 2.2±0.8 for treated islets versus 1.8±0.8 for untreated islets, $P=0.2$). The IPGTT demonstrated a higher glucose excursion in untreated mice as compared to treated mice (AUC glucose: 1273 mmol/120min for treated mice versus 2804 mmol/120 min for untreated mice, $P=0.03$). Also, the IPGTT stimulated human C-peptide excursion was greater in mice who received islets treated with diazoxide than in mice who received islets without diazoxide exposure (0.34±0.23 nmol/l vs 0.056±0.10 nmol/l at 60 min, respectively, $P=0.03$).

Conclusion

Diazoxide pretreatment of isolated human islets improves pancreatic islet survival *in vitro* and leads to improved islet graft function in diabetic mice.

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GP114

Benefits of the association of triiodothyronine (T3) to insulin treatment for the glycemic control of alloxan-induced diabetic rats

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Diabetes mellitus (DM) is a disease that results from impairment of insulin synthesis/secretion or signaling. The glycemia of type 1 DM (DM1) patients is controlled by insulin replacement therapy, which chronically results in insulin resistance. We have shown that alloxan-induced diabetic rats present hypothyroidism, and that T3 treatment reduced the inflammatory state and hepatic glucose production and increased insulin sensitivity, improving glycemia control. Considering that insulin replacement is the unique treatment for DM1 and that T3 was shown to increase insulin sensitivity in DM1 rats, this study aimed at investigating whether T3 could act as an adjuvant of insulin for DM1 treatment. Male Wistar rats (250 g) were made diabetic with alloxan injection (150 mg/kg, ip), and assorted in different groups that were subjected to insulin treatment (3 or 6 U) associated or not with T3 (1.5 µg/100 g de PC), for 4 weeks. Non-diabetic rats were subjected to the same procedures, but treated with saline instead of T3 and/or insulin. They were weekly weighted, and subjected to the evaluation of fasting glycemia. The insulin sensitivity was evaluated by the constant rate for the Insulin Tolerance Test (kITT). It was shown that DM rats treated or not with T3 presented lower body weight (BW) than control group and insulin treated group. kITT returned to control levels when DM rats were treated with 3 or 6U of insulin or with 3U of insulin plus T3. However, the kITT was reduced when DM rats were treated with 6U of insulin plus T3. The fasting glycemia of DM rats was higher than those observed in all groups studied. The fasting glycemia of DM rats treated with insulin (both doses) and/or T3, was lower than non-treated DM rats. Our findings reinforce that T3 treatment improves insulin sensitivity and fasting glycemia of DM rats, and show that the association of T3 with insulin in the lower dose (3U) ameliorates glucose homeostasis, since it reduces the fasting glycemia and increases the kITT to the levels of the control group, restoring the insulin sensitivity. We conclude that T3 could act as an adjuvant of insulin (3U) in the DM treatment. The implication of this data is that with this association lower doses of insulin could be used for the DM treatment, which would postpone the development of insulin resistance that classically occurs in patients under insulin chronic treatment.

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GP115

Male AKR1D1 (5β-reductase) knockout mice have altered pancreatic islet morphology and hormone secretion

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The enzyme 5β-reductase (AKR1D1) catalyses an essential step in bile acid (BA) synthesis, but in addition, controls intra-cellular steroid hormone availability by inactivation. Steroid hormones and BA are regulators of global lipid and carbohydrate metabolism. As disturbances in steroid hormone and BA metabolism have potent effects on metabolic health, we hypothesize that AKR1D1 may play a role in metabolic homeostasis. The role of AKR1D1 in regulating glucose homeostasis and pancreatic function remains unexplored. We generated a global AKR1D1 knockout (KO) mouse and using immunohistochemical and stereological techniques, defined whole pancreas and islet morphology in mice at 12 weeks of age (12w) compared against wild-type (WT) controls. Additionally, pancreatic islets were isolated from male WT and KO mice at 30w. Insulin and glucagon secretion were assessed in static incubations. At 12w, relative pancreas mass was decreased in AKR1D1 KO mice compared to WT controls, in both males (g/kg: WT: 12.7±1.3, KO: 7.5±1.0) and females (g/kg: WT: 9.2±0.7, KO: 6.3±0.2, $P<0.05$). Pancreatic islet volume and relative beta-cell mass were decreased in male KO mice only. At 30w, insulin secretion was increased in isolated KO islets upon treatment with 1mM (basal) glucose (mean as % islet content: WT: 0.07±0.01, KO: 0.12±0.01, $P<0.05$), without any change in total islet insulin content. However, in response to 20 mM glucose, the increase in insulin secretion was lower in KO islets when expressed relative to basal (WT: 3.5-fold change, KO: 2.6-fold change, $P=0.08$). Compared to WT controls, the KO islets failed to suppress glucagon release in the presence of 20 mM glucose (mean as % change in glucagon secretion: WT: −29±20, KO: 61±14). Indeed, we observed a paradoxical increase in glucagon secretion with increasing glucose concentration (1 mM glucose; WT: 5.8±1.1, KO: 7.4±3.9 pg/islet per hour. 20 mM glucose; WT: 4.0±0.7, KO: 8.7±3.0 pg/islet per hour). Whilst endogenous expression of AKR1D1 in the murine pancreatic islet is very low, alterations in steroid hormone and BA exposure modifies pancreatic islet cell function. AKR1D1 KO male mice have a dysregulation of insulin and glucagon secretion, which may have profound effects on normal glucose homeostasis. The mechanisms underpinning the changes observed remain to be determined. Further characterization is warranted to define the role of AKR1D1 and to determine whether it has potential as a therapeutic target in metabolic disease.

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GP116

The role of oncostatin m in the development of type 2 diabetes associated with obesity

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Background

Obesity can lead type 2 diabetes (T2D), however there are patients with obesity who present euglycemia. The mechanisms by which T2D appears have not been fully elucidated. Oncostatin m (OSM) is a proinflammatory cytokine, member of the IL-6 family, which is increased in obesity in mice and humans, and impairs browning in mice. Here, we aim at evaluating the potential role of OSM in the development of T2D in patients with obesity.

Material and methods

A cohort of 25 patients across a range of BMI (24–60 kg/m^2) were recruited for this study. Patients were classified in 3 groups according to clinical data: 1) Healthy normal-weight controls; 2) Normoglycemic obesity (fasting glycemia <100 mg/dl); 3) Hyperglycemic obesity (fasting glycemia >100 mg/dl). Subcutaneous white adipose tissue (sWAT) was collected for RNA analysis.

Results

As expected, we found that OSM mRNA levels increased in sWAT from patients with obesity compared to healthy controls. Moreover, we observed for the first time that OSM mRNA expression was elevated in patients with obesity who had hyperglycemia compared to those who had obesity but normal glucose values ($P=0.04$). In addition, a direct correlation was found between OSM gene expression and insulin and triglyceride levels.

Conclusions

Low-grade chronic inflammation during obesity may lead to the development of T2D. OSM is a cytokine with an important role in several inflammatory diseases. Here, we propose that this cytokine could also be involved in the development of insulin resistance. Therefore, OSM might be a novel target molecule for the prevention/treatment of T2D associated to obesity.

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Endocrine Case Reports

GP117

A rare case report of Graves disease with coexisting TSH producing pituitary adenoma

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Background
Only 10 cases of Grave's disease coexistencing with a TSH-secreting pituitary adenoma (TSHoma) have been reported to date. We present a patient with a TSHoma identified based on the biochemical pattern developing while on treatment with anti-thyroid medications initiated after establishing the diagnosis Grave's disease.
Case report
A 44-year-old Caucasian lady presented with unintentional weight loss. Physical examination revealed diffuse goiter without bruit. TSH was 0.158 (0.4–4.5, free T4 (FT4) 3.5 mg/dl (0.8–1.8) with TSI antibodies elevated 345%. I^{123} thyroid uptake and scan showed a diffuse uptake of 84% at 24 h. While on treatment with Methimazole(MMI), thyroid function tests (TFTs) normalized initially, however, a pattern of elevated FT4 with inappropriately normal TSH was noted. Assay interference and thyroid hormone resistance were ruled out by negative HAMA antibodies and negative RTH mutation analysis. Alpha subunit was1.2 ng/ml (normal <1.02) with elevated α-TSH/TSH molar ratio at 5 (normal range <1). MRI revealed a $1.7\times1.4\times1.6$ cm pituitary macroadenoma. Transsphenoidal resection of the pituitary adenoma was done. TFTs normalized postoperatively without medications. However, four months after surgery, FT4 was found to be elevated at 6.5 with suppressed TSH <0.005. Patient was treated again with MMI with successful achievement of biochemical and clinical euthyroid state. Discussion: Hyperthyroidism caused by excess TSH is uncommon. TSH-secreting pituitary adenoma accounts for less than 2% of pituitary adenomas. The association of TSHoma with Graves' disease is exceedingly rare.. It is recommended that surgery as primary therapy for TSHoma but there is no established management guideline for coexisting condition of Grave's disease and TSHoma at this time. In our case, it is possible that the coexistance of the two conditions is incidental. However, the interruption of normal negative feedback mechanism caused by antithyroid medications leading to the progression of preexisting TSHoma has been postulated. Similarly, it has been postulated that a rapid decrease TSH level after pituitary tumor removal may induce autoimmune activation against the thyroid gland
Conclusion
We emphasize the importance of re-evaluation of the primary diagnosis and consideration of coexisting diagnoses including rare entities if there is any deviation of clinical and laboratory findings from the primary diagnosis.

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GP118

Abstract withdrawn.

GP119

Non-syndromic multiple insulinomas with atypical clinico-biological presentation in two adult patients: a specific entity?

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Introduction
Insulinoma is the most frequent functional endocrine tumor of the pancreas but remains rare with an incidence of less than 5 cases by million and by year. It is often sporadic but can occur in the context of MEN1 in about 5% of cases, being then readily multiple. Clinically, it is typically responsible for fasting hypoglycemic episodes. Only one case of multiple insulinomas, with no obvious argument for MEN1 context, has previously been reported (Babic an al., *JCEM*, 2016).
Methods
We report two cases of multiple insulinomas with atypical clinical and biological presentation, occurring outside the context of MEN1. The first case was a man, 51 years old and the second case, a woman, 69 years old. Both patients reported post-prandial hypoglycemic episodes and experienced severe hypoglycemia following glucose charge, respectively 0.8 mmol/l after intravenous glucose load in the first case and 2 mmol/l after oral glucose charge in the second case, with concomitant elevated insulin, respectively 157.6 mUI/l and 28.2 mUI/l. More expectedly, both cases also displayed at least one hypoglycemic episode during fasting trial, always associated with inadequate insulin and C-peptide levels, confirming the existence of an endogenous hyperinsulinism. Pancreatic imaging (MRI or CT) identified 4 lesions in the caudal region of the pancreas in both patients, ranging from 3.5 to 12 mm in the first case -2 of them being confirmed by octreoscan- and ranging from 8 to 30 mm in the second case-all harboring intense signal on TEP-DOTATOC (negative octreoscan). Histology confirmed the presence of 4 neuroendocrine benign tumors in both cases, respectively all and three of them being positive for insulin staining. No mutation in MEN1 gene or in genes involved in hyperinsulinism including ABCC8, KCNJ11, GCK, HNF4A and HNF1A was identified in the first case while MEN1 gene analysis is still in progress for the second case (very unlikely diagnosis).
Conclusion
We describe here a new entity of non-syndromic multiple insulinomas. Symptoms begin after the age of 50 years old, consisting in hypoglycemic seizures, unusually post-prandial. Glucose charge, stimulating inadequate insulin secretion, reproduces severe hypoglycemia. Organic substratum consists in lesions, localized in pancreas tail and positive in molecular imaging based on somatostatin receptors expression. The search for a molecular alteration might give clue to this new entity.

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GP120

Langerhans cell histiocytosis: diagnosis on thyroid aspirate

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Langerhans cell histiocytosis (LCH) is a disease with monoclonal proliferation and infiltration of organs by Langerhans cell. LCH is commonly seen in the skeletal system and skin, but it may also involve paranchymal organs. Thyroid involvement in LCH is unusual, and coexistence of thyroid with lung involvement is seen very rare. Here we present a patient with LCH, who has thyroid and lung involvement.
Case
A 26-old woman, who had LCH of the lung was referred to our clinic for thyroid nodules detected on Thorax computerized tomography. She had no symptoms at admission. On physical examination no pathological findings were detected. No goitre was seen on the examination of the neck. Thyroid function showed subclinical hypothyroidism based on the following hormone levels: free triiodothyronine (FT3): 2.4 pg/ml; free thyroxine (FT4):0.97 ng/dl and TSH: 12.30 mIU/l; antithyroid antibodies were negative. Levothyroxine was prescribed, and the thyroid function returned to normal. On thyroid ultrasound, the right lobe measured $11\times10\times40$ mm and the left lobe measured $10.7\times13\times40$ mm. On the left lobe a $5\times6\times14$ mm hypoechoic area was detected (Figure 1). Fine needle aspiration and biopsy was performed from this area. On pathological analysis proliferation of Langerhans histiocytes with nuclear grooves in a background of scattered eosinophils was detected. Immunohistochemical staining for S-100, CD68 and CD1a were positive. Chemotherapy was administered to the patient.
Discussion
LCH is a rare neoplastic disease of the langerhans cells, which may involve various organs and systems. Thyroid involvement of LCH is rare with only a slow

number of patients reported in the literature. The frequency of thyroid involvement was reported as 0.4% among all LCH patients. Diagnosis of thyroid LCH is quite challenging, but thyroid involvement of LCH should be kept in mind in patients suffering from LCH.

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GP121

Coexistence of papillary thyroid cancer and malignancies of other organs in patients carrying CHEK2 gene mutations – case series.

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Introduction
CHEK2 mutations are associated with increased risk of having neoplasms of various organs, including thyroid, breast, colon, renal and ovarian cancers. Coexistence of thyroid and breast cancers was observed in female carriers of CHEK2 gene mutations. In polish population the most common mutations are those truncating CHEK2 protein (1100delC, IVS2+1G>A, del5395) and a missense I157T CHEK2 mutation. Carrying missense I157T mutation is connected with having twice the risk of getting papillary thyroid cancer in polish population whereas mutations truncating CHEK2 protein increase the risk by five times.
Case series
1) 63-year-old female patient after total thyroidectomy because of multifocal papillary thyroid cancer in 2014, after surgery in 2002 and subsequent hormonal therapy because of left-sided breast cancer and after surgery because of sigmoid colon cancer in 2013. In family history – mother suffered from breast cancer. Molecular testing revealed missense I157T mutation of CHEK2 gene.
2) Female patient, operated in 2013 at the age of 44 for multifocal papillary thyroid cancer with metastases to the left-sided cervical lymph nodes. In October 2013 the patient was diagnosed with invasive ductal left-sided breast cancer with metastasis to the left axillary lymph node. She was treated with breast amputation, radiotherapy and hormonal therapy. Molecular testing revealed missense I157T mutation of CHEK2 gene.
3) 60-year-old female patient after total thyroidectomy in 2017 because of papillary thyroid cancer, after right-sided mastectomy in 2010 because of breast cancer and after surgery because of endometrial cancer in 2011. Molecular testing revealed CHEK2 protein truncating mutation.
4) 49-year-old female patient after total thyroidectomy in 2017 because of papillary thyroid microcarcinoma, after left-sided mastectomy in 2015 because of breast cancer. Molecular testing revealed CHEK2 protein truncating mutation.

Conclusions
1) In consideration of possible coexistence of thyroid and breast cancers, in case of diagnosing one of them, it is advised to perform diagnostics and observation to identify possible development of the other neoplasm.
2) In patients with CHEK2 gene mutation we need to remember about higher risk of papillary thyroid cancer and possibility of concomitant malignancies especially breast cancer.

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GP122

A case of nivolumab induced fulminant type 1 diabetes

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Introduction
Immunotherapy has revolutionized the treatment of cancer. Nivolumab, an anti-programmed cell death 1(PD-1) antibody, is used to treat several malignancies refractory to standard chemotherapy. While highly effective at prolonging patient survival, these agents can induce a wide range of endocrine immune-related adverse events (irAEs), including hypophysitis, thyroid dysfunction, and, uncommonly, type 1 diabetes (T1DM). Here we describe a rare case of PD-1 inhibitor induced fulminant type 1 diabetes (FD).Case Report:A 55-year-old African American female was diagnosed with stage III B squamous cell carcinoma of the lung in 2013. She was not a surgical candidate and received 6 cycles of carboplatin and gemcitabine as well as salvage radiation. One year later, there was disease progression with involvement of the brain, adrenal glands, and gluteal muscle. In 2015 she began treatment with nivolumab. Cycle 4 was delayed, as she developed autoimmune hepatitis, for which she received high dose steroids. After normalization of liver function tests, nivolumab was restarted. After 8 months, she presented for cycle 13 reporting extreme fatigue, dry mouth, nausea, polyuria and polydipsia. Laboratory tests at the time of hospitalization revealed a blood glucose of 467 mg/dl (70–105). She had ketonuria without ketoacidosis. Unexpectedly, her glycosylated hemoglobin (HbA1c) was only 7.1%, suggesting rapid onset of hyperglycemia. Serum anti-glutamic acid decarboxylase antibody and anti-islet-cell antibody were negative, and C-peptide was 0.42 ng/ml (0.8–3.85), consistent with a diagnosis of FD. HLA-typing was not performed. Insulin therapy was initiated, and she was discharged on a basal/bolus insulin regimen. Given wide glycemic excursions, the patient was eventually transitioned to insulin pump therapy with a continuous glucose monitor. Nivolumab was not restarted.
Discussion
FD is a severe subtype of T1DM, characterized by the complete loss of pancreatic beta cells at disease onset. Initially described in Japan in 2000, cases have been reported primarily in East Asia. FD is characterized by rapid onset of hyperglycemia combined with ketoacidosis or ketonuria and the absence of islet-cell autoantibodies. Out of the 24 cases of diabetes thus far reported as a side effect of anti-PD-1 treatment, 10 (42%) are consistent with FD, with unusually low HbA1c at diagnosis (under 8.7%) and low or undetectable c-peptide. Given increasing oncologic indications for anti-PD1, it is important that physicians be made aware of this rare, but potentially life-threatening, adverse reaction. Frequent biochemical monitoring and early recognition of hyperglycemia are critical in optimizing treatment outcomes.

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GP123

A rare case of type-2 familial partial lipodystrophy (FLD type 2) non-Dunnigan type with laminin A/C gene (LMNA) mutation causing multi-organ failure and diabetes mellitus

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Introduction
Mutations of the LMNA gene cause a wide range of diseases including lipodystrophy, myopathy [including dilated cardiomyopathy (DCM)], neuropathy and progeroid syndrome, and are collectively known as A-type laminopathies.
Case report
A 51-year-old Caucasian male with history of heart, liver and kidney transplants was referred for evaluation and treatment of post-transplant diabetes. He was diagnosed with hypertriglyceridemia at age 38. At 43, he was diagnosed with idiopathic cardiomyopathy. Subsequently, he developed liver failure that was presumed to be secondary to passive congestion from heart failure. He underwent simultaneous heart and liver transplants at 44. By age 51, he developed end stage renal disease, treated with hemodialysis prior to recent renal transplant. He developed post-transplant diabetes and endocrine consult was requested. He was noted to be extremely thin with BMI 17.4 kg/m^2 (weight = 130 lbs, height = 6′1″), with generalized lipodystrophy including face, trunk and extremities. Diabetes was managed with a basal/bolus insulin regimen requiring approximately 1.8 units of insulin/kg to control hyperglycemia suggesting severe insulin resistance. Laboratory evaluation was notable for leptin of 2.5 ng/ml (0.3–13.4). Genetic testing revealed a heterozygous *LMNA* gene missense mutation (c.1045 C>T; p. Arg349Trp). Since identification of the mutation, metformin was added to the insulin with the goal of improving insulin resistance.
Discussion
To date, 19 additional patients have been reported with the c.1045C>T *LMNA* mutation identified in our patient, including a family with 16 affected members, of whom 4 had renal disease. Patients with c.1045C>T mutations have partial lipodystrophy of the non-Dunnigan type (affecting face and extremities), with the exception of one with Dunnigan-type. In the 19 patients, DCM was noted in less than half and elevated creatine kinase, with or without clinical signs of myopathy, was also noted. Less than half had overt diabetes and at least one had euglycemic insulin resistance. The c.1045 C>T variant was not observed in the NHLBI Exome sequencing project, 1000 Genomes Project or Exome Aggregation

Consortium database; however the p.Arg349Trp substitution has been identified in patients with skeletal, cardiac and metabolic phenotypes. Collective evidence supports c.1045 C>T as a likely pathogenic variant for an A-type laminopathy and the multiorgan failure seen in our patient. Multiorgan failure should alert endocrinologists of the possibility of *LMNA* mutation.

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GP124

MODY – a diagnosis to be considered in diabetes

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Introduction
Maturity-Onset Diabetes of the Young (MODY) is a form of monogenic diabetes caused by mutations in islet-related genes characterized by early-onset and inheritance in an autosomal dominant manner. MODY accounts for 2 to 5% of all cases of diabetes. The clinical presentation is heterogenous. Our aim was to characterize clinical features of patients with MODY in our department.
Methods
We retrospectively analysed MODY diabetes cases diagnosed at the Endocrinology Pediatric Unit (EPU) and at the adult Endocrinology Department (ED) of our hospital, from 2000 to 2017.
Results
We found 8 patients diagnosed at the EPU and 4 at the ED adult. Two pairs of them are sisters. The majority are female ($n=10$), with an average age at diagnosis of 12 years-old (IQR 7-16). All had family history of diabetes. Genetic confirmation of MODY was obtained 48 months after clinical diagnosis of diabetes (IQR 19-77). None presented diabetic ketoacidosis at diagnosis. Negative islet autoantibodies were observed in all. The median HbA1c at diagnosis was 7.5% (IQR 6.4–8.3). Regarding the type of MODY, 8 presented GCK mutation (MODY 2), 3 HNF1A mutation (MODY 3) and 1 HNF1B mutation (MODY 5). In patients with MODY 2, one is not currently under oral antidiabetic drugs, one is treated with insulin and the remaining with metformin and/or dipeptidyl peptidase-4 inhibitor. The 3 patients with MODY 3 are under a sulfonylurea and the patient with MODY 5 is treated with insulin in a basal bolus scheme.
Discussion
The diagnosis of MODY requires a high index of suspicion. Therefore, in a patient with family history of diabetes, negative islet autoantibodies and diabetes onset <25 years, a diagnosis of MODY should be suspected. Our series revealed a considerable delay until the confirmation of MODY, which supports the increased awareness warranted for this entity.

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GP125

Hyperinsulinaemic hypoglycaemia in the three generations of a family with GCK, c.295T>C (p.Trp99Arg) mutation

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Background
Familial Hyperinsulinaemic hypoglycaemia (FHH) is a very rare disease with heterogeneous clinical manifestation causing risk of late diagnosis or even misdiagnosis. In infants and children, it can lead to serious and permanent damage to the central nervous system. FHH has been correlated with mono-gene mutations in approximately 48% of cases. Clinical manifestation may vary even in the same affected GCK mutation family.
Objective
To describe the clinical presentation and metabolic profiles of affected family members with GCKc.295T>C(p.Trp99Arg) mutation.
Design
Clinical, biochemical and metabolic assessment, and GCK sequencing in affected family members.
Results
Family G: four family members from three generations affected (father, 2/3 children, grandson). A father of three children, age 54 (birth weight 3800g, current BMI-32), diagnosed at the age of 20 years. Symptoms of hypoglycaemia (HS) present from postnatal period, with an increased intensity in early childhood. Learning and behaviour problems during childhood. Hypoglycaemias:mild/severe, fasting/after the meal, no relation with physical activity/diet. Epilepsy diagnosed at age 10. Diazoxide: from the age of 20/some improvements/poor compliance. MRI/GLP-1 imaging not significant. Normal lipids/no liver steatosis. A son, age 25 (birth weight 4400 g, current BMI-25.9), diagnosed at the age of 4 years. HS from postnatal period, increased intensity in early childhood. School difficulties/problems with concentration. HS: mild/severe, fasting/overnight hypoglycaemias/after the meal/improvement after carbohydrate rich diet, no relation to physical activity/diet. Diazoxide: from age of 4, partial improvement/poor compliance. MRI not significant. Normal lipids/no liver steatosis. A daughter, age 23 (birth weight 3650 g, current BMI-23), diagnosed during postnatal period. HS: mild/severe, increased in early childhood. School difficulties/problems with concentration. HS: fasting/ after the meal, no relation with physical activity/diet. Diazoxide from postnatal period, some response/poor compliance. MRI not significant. Normal lipids/no liver steatosis. During early pregnancy (2014) severe hypoglycaemias, with response to steroid therapy, in the second/third trimester improvement. A grandson, age 3 (birth weight–3850 g, glucose after delivery 15 mg%). Immediate treatment with Diazoxide, no HS. Physical/psychological development is normal.
Conclusions
The clinical presentation of the disease is similar in the family members with GCK c.295T>C (p.Trp99Arg). Early diagnosis, diazoxide implementation/compliance are important in the course of the disease.

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GP126

Acromegaly and acromegaloidism, two rare insulin-resistance conditions in one patient: reason for GH-IGF-1 discrepancy?

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Introduction
Lipodystrophies are a group of genetic or acquired diseases characterized by abnormal adipose tissue deposition, frequently associated with insulin resistance, diabetes mellitus, dyslipidaemia, hypertension and hepatic steatosis. Congenital generalized lipodystrophy (LCG) is a well-defined syndrome with autosomal recessive heredity, prevalence <1:10million, with about 400 cases being described. Extreme shortage of subcutaneous adipose tissue, muscle hypertrophy and other adipose tissues, confer an acromegaloid-like appearance in patients with LCG, however no case of SBS and acromegaly has been reported.
Clinical case
63-year-old man appealed to endocrinology clinic for suspected lipodystrophy. He had lipoatrophy of upper and lower limbs, muscular prominence, acromegaly facies with thick lips, widening of the wings of the nose, creased nasolabial grooves, dental diastema, prominence of supraciliary arches, large hands and feet and soft tissue tumescence. No acanthosis nigricans. None of the parents had changes in body composition or diabetes. His 59-year-old sister has similar phenotype. He had dyslipidaemia (total-cholesterol: 192 mg/dl, HDL:31 mg/dl, LDL1: 41 mg/dl, triglycerides: 440 mg/dl); increased IGF-1: 379–481–410 ng/mL (NL<269); HOMA-IR: 11.93, A1c:6.4%. 1st OGTT: Impaired glucose tolerance (0 h:101; 2 h:186 mg/dl) and GH-0h:1.5; nadir:0.92 ng/ml; second OGTT 10 months after-diabetes (glucose 0 h:120; 2 h: 204 mg/dl) and GH-0h:0.98; nadir: 0.64 ng/ml). Thyroid function, gonadal, metabolism calcium phosphate, prolactin, ACTH, and cortisol are normal. There was a ratio of fat mass trunk/limbs to 1.02 by densitometry and without osteoporosis. Colonoscopy and upper digestive endoscopy were normal. A 17 cm hepatomegaly with mild steatosis was detected on abdominal ultrasound. Left ventricular hypertrophy was observed in the ECG. In the pituitary MRI was found an area of hypocaptation contrast product with rounded aspect in right half of pituitary gland, passing

midline to opposite side and prophesying to sphenoid sinus in relation to the pituitary adenoma. No deviation of the pituitary stalk. Subjected to transphenoidal pituitary surgery pathological evaluation showed pituitary adenoma, with extensive expression of GH and ACTH and rare expression of FSH and PRL. Genetic study revealed a intron3/exon3 deletion of the AGPAT2 gene in homozygosity. A GH/IGF-1 discrepancy, IGF-1 increased with normal GH variant was present. The role of insulin resistance or hepatic steatosis isn't clear and could disturb the diagnosis.

Conclusion

GCL is a rare disease that occurs with acromegaly; however, no case of genetic lipodystrophy associated with acromegaly has been described in the literature.

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Female Reproduction

GP127

Cardiovascular disease in a nationwide population of Danish women with polycystic ovary syndrome

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Background

Polycystic ovary syndrome (PCOS) is associated with obesity and low grade inflammation, factors linked to cardiovascular disease (CVD).

Methods

National Register-based study including women with PCOS and no previous diagnosis of CVD or hypertension. PCOS OUH ($n=1165$) included premenopausal women with PCOS and clinical and biochemical examination. PCOS Denmark ($n=18\,112$) included women with PCOS in the Danish National Patient Register. Three age-matched controls were included per patient ($n=52\,769$). The main study outcome was CVD events including hypertension defined according to nationwide in- and outpatient hospital contact diagnosis codes and/or inferred from filled medicine prescriptions.

Results

The age at inclusion was median (quartiles) 29 (23–35) years and follow up was 11.1 (6.9–16.0) years. The Hazard ratio (95% CI) for development of CVD including hypertension in PCOS Denmark was 1.7 (1.6; 1.8) ($P<0.001$) and the total event rate of CVD was 19.2 per 1000 patient years in PCOS Denmark vs 11.6 per 1000 patient years in controls ($P<0.001$). The median age at diagnosis of CVD was 35 (29–42) years in PCOS Denmark vs 36 (30–44) years in controls ($P=0.02$). Obesity, diabetes, and infertility, and previous use of oral contraceptives were associated with increased risk of development of CVD in PCOS Denmark ($P<0.001$). Also, age, BMI, blood pressure, lipid status, and glycemic status predicted development of CVD in PCOS OUH.

Conclusion

The event rate of CVD and hypertension was higher in PCOS compared to controls. The risk of developing CVD must be considered even in young women with PCOS.

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GP128

Low-dose SKA Progesterone and Interleukin-10 modulate the inflammatory pathway in endometriotic cell lines

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Endometriosis is a chronic gynecological inflammatory disease characterized by the presence of functional endometrial glands and stroma outside of the uterine cavity. It affects 7–10% of women of reproductive age, up to 50% of women with infertility and up to 60% of women with dysmenorrhea. The aim of this preclinical study was evaluate the efficacy of low-dose SKA Progesterone (GUNA) and low-dose SKA IL-10 (GUNA) in the modulation of the inflammatory response in endometriotic cell lines. Immortalized human endometriotic epithelial cells (12Z) derived from active red peritoneal lesions, immortalized human endometriotic stromal cells (22B) derived from active red peritoneal lesions and immortalized human endometrial cell line T-Hesc (ATCC collection) have been used for this study. Cells were treated with SKA-Progesterone and SKA-IL10 at low doses (10 pg/ml and 10 fg/ml respectively). Medroxyprogesterone 17-acetate (MPA) was used at a dose of 10 μM as reference treatment. We analyzed the modulation of HSD17B1 levels by WB analysis after low-dose SKA Progesterone and MPA and the modulation of IKBα protein levels and NF-kB p65 nuclear levels by WB analysis after low-dose SKA-Progesterone, low-dose SKA-IL10, low-dose SKA-Progesterone and low-dose SKA-IL10 (combined treatment), MPA. Low-dose SKA Progesterone was effective in the inhibition of HSD17B1 expression in endometriotic epithelial (12Z) and stromal (22B) cell lines. Low-dose of SKA Progesterone and low-dose of SKA-IL10 inhibit NF-kB p65 nuclear localization and DNA binding in endometriotic epithelial (12Z) cells, stromal (22B) cells line and in endometrial cell line T-Hesc. The combined treatment showed an additive effect, namely increasing the inhibition of nuclear localization of NF-kB p65 and DNA binding as result of single treatments. Our data suggest that the use of a combination of low-dose SKA Progesterone and IL-10 may represent an opportunity for the development of new therapies in the clinical management of endometriosis.

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GP129

Impaired GLP-1 response predicts prediabetes in obese PCOS with adverse metabolic phenotype independent of BMI

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Objective

Impaired glucose homeostasis in PCOS is closely linked to obesity, age and disease phenotype. The potential separate role of reduced GLP-1 response in the development of prediabetes in this population is unclear.

Aim

To compare the GLP-1 response after OGTT in a cohort of obese PCOS with normal glucose tolerance (NGT) and prediabetes.

Design/participants/methods

Case control study recruited 26 obese Caucasian women with PCOS phenotype A. Thirteen of them had normal glucose tolerance (NGT) and 13 had prediabetes defined as having impaired fasting glucose, impaired glucose tolerance or both. They were matched for BMI (37.0 ± 5.5 kg/m^2, mean ± S.D.) and age (37.2 ± 6.9 years, mean ± S.D.). Serum glucose, insulin, C-peptide, total GLP-1 and total GIP were sampled during 2 h OGTT. Model derived static and dynamic parameters for the assessment of beta cell function and insulin resistance were determined. All patients underwent measurement of androgen profile and whole-body composition by DXA.

Results

Women with prediabetes had significantly reduced total GLP-1 after glucose load (GLP-1 in 120 min 3.3 ± 2.1 vs 5.5 ± 2.7 pM in NGT, $P=0.014$) and decreased incremental area under the curve of GLP-1 ($\Delta AUC_{GLP\text{-}1}$) when compared to NGT group ($P=0.016$). Values of GLP-1 at 120 min below 3.02 pM predicted prediabetes (sensitivity 0.615 and specificity 0.923). In addition, women with prediabetes had lower insulin and C-peptide values with significant difference at 90 and 120 min of OGTT ($P=0.01$) and lower insulin sensitivity index (OGIS) (387 ± 69.5 vs 326.6 ± 59.7 in NGT, $P=0.04$). Despite same BMI, group with prediabetes had higher visceral adipose tissue (VAT) mass, volume and area as measured by DXA ($P=0.001$ for all). Plasma GLP-1 levels at 120 min was negatively correlated with VAT mass and volume and positively correlated with OGIS. Furthermore, the correlation between the $\Delta AUC_{GLP\text{-}1}$ and the family history of at least one first-degree relative affected with type 2 diabetes was confirmed. The two groups did not differ in total GIP, HOMA-B, MBCI, QUICKI, HOMA-IR and IAI and androgen profile.

Conclusion

GLP-1 response to oral glucose was reduced in obese PCOS with prediabetes independent of age, BMI and disease phenotype. Our findings identify a new separate risk factor for prediabetes in obese PCOS, in particular with predominant visceral obesity.

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GP130

Alterations in gonadotropin receptors and signal activation in granulosa lutein cells from women with polycystic ovary syndrome

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Background
Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting 5–10% of women of reproductive age. The underlying pathogenesis is complex and incompletely understood. There is evidence that gonadotropin and gonadotropin receptor action play a role in the pathogenesis of PCOS with genome wide association studies in PCOS also implicating altered gonadotropin action in the aetiology of PCOS. Furthermore, our recent studies have demonstrated that gonadotrophin receptor signaling is tightly regulated by the endocytic pathway. However, the precise mechanisms resulting in altered gonadotropin receptor activity in PCOS are unclear.
Objectives
1. To measure gene and protein expression of LH/hCG and FSH receptors in granulosa lutein cells (GLC) from women with and without PCOS. 2. To measure in-vitro second messenger cAMP generation in GLC from women with and without PCOS after treatment with FSH and LH. 3. To assess the role of receptor internalization on signalling in GLC from women with and without PCOS.
Materials and methods
GLC were isolated from follicular fluid collected at the time of oocyte retrieval. RNA was extracted from the cells and gene expression analysed by RT-qPCR. Protein was extracted and expression analysed by immunohistochemistry. GLC were cultured and treated with LH or FSH with or without pre treatment with Dyngo-4a, a dynamin inhibitor, and cAMP assay performed.
Results
Gene and protein expression of LH/hCG receptor and it's known splice variants were similar in GLC from women with and without PCOS. Gene expression of FSHR was higher in GLC from women with PCOS than controls (4-fold, $P<0.05$). LH-dependent cAMP levels were significantly higher (2.5 fold, $P<0.05$) in GLC from women with PCOS compared to control. Pre-treatment of GLCs with Dyngo4a, which inhibits dynamin dependent receptor internalisation, inhibited both LHR and FSHR cAMP generation (70–80%) equally in both control and PCOS.
Conclusion
There is higher FSH receptor expression in GLC from women with PCOS. Although gene and protein expression are similar in normal and PCOS GLC, LH/hCG receptor signal activation in GLC from women with polycystic ovary syndrome is amplified. Receptor internalisation is required for normal cAMP generation in both normal and PCOS GLCs.

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GP131

Prevalence of mutations in the insulin receptor gene and lamin A/C gene in functional ovarian hyperandrogenism with insulin resistance

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Introduction
Extreme insulin resistance monogenic syndromes, including type A insulin resistance syndrome and congenital lipodystrophies, share some phenotypic characteristics with polycystic ovary syndrome (PCOS). These conditions have an increased risk for developing cardiovascular disease and diabetes mellitus. Thus, both an early diagnosis and a personalized management are required at clinical realm.
Objective
To assess the prevalence of mutations in the insulin receptor (*INSR*) and lamin A/C (*LMNA*) genes in women with functional ovarian hyperandrogenism and insulin resistance.
Material and methods
n: 242 women with functional ovarian hyperandrogenism (PCOS or idiopathic hyperandrogenism) and insulin resistance defined by a Matsuda-index (ISI) <3.5 and/or HOMA-IR$>$ 3.2 were studied. Genetic analysis was performed with genomic DNA from total blood samples using the real-time polymerase chain reaction (PCR) technique with fluorescence TaqMan probes or by sequencing. Mutations described in the literature in *INSR* and *LMNA* genes were screened in all patients. In 49 extreme-insulin resistant patients, exons and adjacent intronic regions of *INSR* and *LMNA* genes were also studied by Denaturing High-Performance Liquid Chromatography (DHPLC), and positive results were confirmed by sequencing.
Results
Sequencing of amplified DNA revealed that found variants in exons 2, 8, 9, 12, 13 and 17 in *INSR* gene, and variants in exons 3, 5, 7 and 10 in *LMNA* gene were benign polymorphisms within the coding region. *LMNA* promoter −1030 C/T polymorphism, described as a putative genetic responsible for arterial stiffness in Japanese population, was detected in 17 subjects with CT genotype and in 4 with TT genotype. Two sister were found to have a patogenic heterozygous mutation in exon 8 (c.1444C$>$T, p.Arg482Trp) in *LMNA* gene, and the final diagnosis of Dunningan familial partial lipodystrophy was established. One proband with extreme insulin resistance was found to have a heterozygous mutation in exon 5 (c.1246C$>$T, p.Arg416*) in *INSR* gene. Currently, exons 19-22 of *INSR* gene are being processed.
Conclusions
The identification of monogenic insulin resistance syndromes is essential in patients with apparent functional ovarian hyperandrogenism. Molecular-genetic studies allow an early diagnosis and genetic counseling, and likely, improving their prognosis. Since most available treatments are not fully satisfactory, molecular studies may provide potential novel therapeutic targets.

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GP132

Women with PCOS display reduced cardiac vagal activity which is dependent on metabolic abnormalities

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It has been reported that women with polycystic ovary syndrome (PCOS) show cardiovascular autonomic dysfunction, with reduced parasympathetic (vagal) and increased sympathetic activity, which are known to be independent risk factors for cardiovascular morbidity and mortality. However, it is not yet clear if PCOS *per se* leads to cardiovascular autonomic dysfunction independently of metabolic abnormalities. In a prospective, general population-based follow-up birth cohort ($n=5889$ females), postal questionnaires were sent at ages 14 (95% answered), 31 (81% answered) and 46 (72% answered). Women who reported both oligo/amenorrhea and hirsutism at age 31 and/or diagnosis of PCOS by age 46 were considered as PCOS cases ($n=279$) and were compared with women without PCOS symptoms or diagnosis ($n=1577$). Clinical examinations were performed at age 31 in 3115 women, and at age 46 in 3280 women. The cardiovascular autonomic function was evaluated at age 46 by vagal-mediated heart rate variability (rMSSD) from R-R intervals, spectral power densities (LF: low frequency and HF: high frequency) and spontaneous baroreflex sensitivity (BRS). Both rMSSD and HF describe the vagal activity. The effects of body-mass-index (BMI), hyperandrogenism and metabolic status were assessed by analysis of covariance (ANCOVA) and linear regression analysis. At baseline, vagal activity was significantly lower in women with PCOS compared with controls (rMSSD: 19.5 [12.4; 31.9] vs 24.3 [16.1; 34.8], $P=0.004$ and HF: 172 [75; 399] vs 261 [112; 565], $P=0.002$), and these differences remained significant after adjustment for BMI by ANCOVA. BRS was comparable in PCOS and control women after adjustment for BMI. In the linear regression model, PCOS and BMI both modified rMSSD (for PCOS: $B=-0.108$, 95%CI: -0.207 to -0.008, $P=0.033$ and for BMI: $B=-0.026$, 95%CI: -0.033 to -0.020,

$P<0.001$), but PCOS lost its significance after adjustment for diastolic blood pressure. Then, in the linear regression model for HF, PCOS remained significant after adjustment for diastolic BP (for PCOS: $B=-0.217$, 95%CI: -0.415 to -0.018, $P=0.033$), but then lost its significance after further adjustment for HOMA-IR. Of note, testosterone or free-androgen-index did not modify rMSSD or HF in the linear regression analysis. Women with PCOS display altered cardiovascular autonomic function manifested as decreased vagal activity. However, metabolic status, but not hyperandrogenism, seems to be the strongest contributing factors. These findings indicate that metabolic abnormalities should be screened and efficiently treated in women with PCOS, already early in life, to prevent the development of cardiovascular autonomic dysfunction and cardiovascular diseases.

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GP133

Favorable prognosis of pregnancies in 28 hypopituitary women: Retrospective multicentric study on 39 pregnancies

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Background
Pregnancy in women with hypopituitarism has been described as presenting high risks of maternal and fetal complications but this is only based on 2 small size series.
Objective
To reassess the prognosis of pregnancy in women with hypopituitarism.
Methods
Multicentric, observational, retrospective study including 39 pregnancies in 28 women with gonadotropic insufficiency and at least one other pituitary hormone deficiency followed in the last 22 years in five French tertiary centers. Due to the a multi-disciplinary approach, the substitutive treatment of corticotroph and thyrotropin insufficiencies were followed by endocrinologists. We collected the data regarding infertility management, pregnancy outcome, obstetrical or endocrine complications and new born children characteristics.
Results
28 women with a median age of 30 years (25–41) were included. Pituitary insufficiency was linked to the following lesions and their medical, surgical or radiotherapic treatments: Craniopharyngioma ($n=8$); different adenomas ($n=8$); Sheehan Syndrome ($n=4$); Hypophysitis ($n=3$); Congenital ($n=3$); Rathke cyst (1); Pinealoma (1). Pituitary deficiences were gonadotropic (100%) Thyrotropic (92%) Somatotropic (81%) Corticotropic (64%) Diabetes inspidus (39%). 26 patients with thyrotropin insufficiency were treated by L-thyroxine adjusted during all the pregnancy. 18 were treated by hydrocortisone for corticotroph insufficiency. Pregnancy was obtained by ovarian stimulation by FSH and ovulation stimulation by hCG in all but 4 cases but *in vitro* fertilization was required in only 6 cases (19%). Among 39 pregnancies, 36 live births (92%) (25 singletons and 11 twins) occured, and 3 ectopic pregnancies, 5 miscarriages and 1 intra uterine fetal death were observed. For all births, the rate of caesarean section was 42%: 36% for singletons and 66% for twins. The new-borns were healthy with a median weight of 3120 g (570–4250) and a median length of 50 cm (31–53), 22% were preterm babies (4% for singletons and 58% for twins) and 27% had a low birth weight (12% for singletons and 58% for twins). No maternal complications related to pituitary insufficiency occurred. The pregnancies outcomes were comparable to those in the French population for singleton pregnancies but there were less favorable for twin pregnancies. Five out of six twin pregnancies had at least one perinatal complication with one intrauterine fetal death.
Conclusion
In this study we found a good prognosis of pregnancies in women with hypopituitarism followed in tertiary centers by a multi-disciplinary team. However because twin pregnancies showed more perinatal complications than in the general population ovarian stimulation should be carefully monitored to favor singleton pregnancies.

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GP134

Abstract withdrawn.

GP135

Liquid chromatography-tandem mass spectrometry characterization of a broad serum and salivary steroid profile in classical form of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder among premenopausal women affecting up to 20% of the population. Even though androgen excess is the main diagnostic criterion for PCOS, the evaluation of hyperandrogenemia relies on methods with low accuracy and mainly able to measure total androgen amounts. Liquid chromatography-tandem mass spectrometry (LC–MS/MS) allows high accuracy steroids measurement and if applied to saliva, it also allows the measurement of free or biovalable fractions. We performed seventeen-hours circadian salivary androgens analysis and serum steroids circadian profile in 9 classic PCOS (oligomenorrhea + hirsutism/high testosterone + polycystic ovary morphology) and 7 fertile controls. Subjects woke-up at 0700 h and collected saliva by direct spitting in fasting condition. At 0800 h subjects went to hospital for blood withdrawal, second saliva collection and anthropometric data recording. The blood collection was repeated at 1000 h and 1600 h. Saliva was collected every hour until 2300 h. Daily food intake and menstrual phase were standardized. Steroids were measured by validated LC–MS/MS methods and area under curve (AUCg) was computed. Compared to controls, PCOS girls were younger ($P=0.023$) and displayed higher BMI ($P=0.017$) and waist circumference ($P=0.011$). Both baseline levels and circulating hormones daily exposure were higher in PCOS: testosterone ($P=0.001$; $P=0.006$) androstenedione ($P<0.001$ for both) DHEA ($P=0.004$; $P=0.001$) and 17OHProgesterone ($P<0.001$ for both). Moreover, PCOS group showed higher estrone ($P=0.002$; $P=0.006$) and 17OHpregnenolone ($P=0.013$; $P=0.001$) levels compared to controls. No differences were found for serum cortisol, cortisone, corticosterone, 11-deoxycortisol, progesterone, estradiol and dihydrotestosterone. PCOS displayed higher salivary androgens both at basal levels and in daily exposure: testosterone (4.41 ± 0.96 vs 13.5 ± 6.9 pg/ml, $P<0.001$; 3314.9 ± 1029.7 vs 8328.9 ± 2984.7 AUCg, $P<0.001$) androstenedione (69.6 ± 18.7 vs 162.3 ± 49.9 pg/ml, $P<0.001$; 51829.7 ± 14968.3 vs 125592.7 ± 36501.2 AUCg, $P<0.0001$), DHEA (169.2 ± 100.4 vs 349.1 ± 152.1 pg/ml, $P=0.007$; 113272.3 ± 47145.4 vs 185457.8 ± 67046.8 AUCg, $P=0.018$) and 17OHProgesterone (10.5 ± 4.9 vs. 25.1 ± 10.2 pg/ml, $P=0.010$; below sensitivity limit vs 14643.0 ± 2790.0 AUCg) compared to controls. PCOS subjects displayed high serum testosterone, androstenedione, DHEA, 17OHProgesterone, 17OHpregnenolone and estrone, both at baseline and in daily exposure. Increased serum androgens resulted in high salivary androgens too, showing the salivary androgens profiling as promising tool for non-invasive diagnostic work-up of PCOS patients.

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GP136

Novel mechanisms and genes involved in the pathogenesis of primary ovarian insufficiency (POI) by whole-exome sequencing approach

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The ovarian reserve naturally declines with age, however, 1–2% of women before 40 years experiences a premature exhaustion of the ovarian function and suffers from a fertility defect named Primary Ovarian Insufficiency (POI). The genetic origin of POI is well established and strongly supported by multiple reports of familial cases. To date, thanks to the candidate gene-discovery approach, few X-linked and autosomal genes have been associated to POI onset, but most of 46,XX cases still remain idiopathic suggesting the involvement of new genetic mechanisms. Whole-Exome Sequencing (WES) has been performed in ten POI patients with the extreme phenotype of absent pubertal development (primary amenorrhea), of which 6 familial and 4 sporadic, to reveal rare variants affecting genes implicated in ovarian function. Their relatives have been similarly analyzed as control population, for a total of 24 exomes. Genomic DNA was first extracted by patients and their relatives, then sheared into random fragments of roughly 300 base pairs and those fragments falling in exome regions were enriched by capturing, and finally sequenced. Data analysis consisted of image recognition, base calling, demultiplexing and trimming of adapter sequences, quality control of generated reads and estimation of coverage, alignment of the clean reads to the reference genome. In order to prioritize variants with potentially pathogenetic role in POI, first we focused on rarity and assessed the frequency of each variant in the general population by using the information provided by ongoing large genome projects (such as ExAC, Exome Variant Server, dbSNP browsers). Variants' frequencies $>1\%$ have been considered not rare and filtered out. A total of 18 570 rare variants (including: missense, 86%; nonsense, 3.5%; small indels, 5.6%) have been identified in our selected cohort of patients. The pathogenic level of each identified variant has been predicted *in silico*. A pathway-based analysis was performed through the Reactome software on 1916 genetic identifiers occurring mutated at least once. The overrepresentation analysis revealed enrichment among altered genes in: the Chromatin organization pathway and, consequently, the cell cycle and meiosis pathways; the Extracellular matrix organization and cell-cell communication pathways. Further, one hundred fifty-two coding variants in 117 genes participating in key biological processes within the ovary were identified by WES and therefore result potentially related to the POI onset in our patients. Finally, we observed the presence of at least two variants in distinct genes in all the patients in agreement with the oligogenic nature of POI.

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GP137

Hypothalamo-pituitary-adrenal axis sensitivity in women with polycystic ovary syndrome

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Introduction
Hypothalamo-pituitary-adrenal (HPA) axis dysregulation could be a link between polycystic ovary syndrome (PCOS) and cardiometabolic and psychological complications associated with disease.
Methods
We analyzed 50 women with PCOS according to ESHRE/ASRM criteria [age 28.66 ± 5.61, body mass index (BMI) 21.94 ± 3.38 kg/m^2] and 50 BMI- and age-matched healthy women (control group, CG), (age 28.66 ± 5.63, BMI 22.09 ± 3.70 kg/m^2). In follicular phase of menstrual cycle we analyzed body composition (BC) by bioelectrical impedance, serum fasting glucose, insulin, lipids, morning cortisol levels, ACTH, androgens and cortisol after overnight $Dex_{0.5mg}$ and Dex_{1mg} tests. HOMA-IR and FAI were calculated. Repeated measures ANOVA was used for analysis of HPA axis fuctionality after Dex tests.
Results
PCOS and CG didn't differ in BC parameters, HOMA-IR and lipids. Morning cortisol was significantly higher in PCOS (476.12 ± 168.68 nmol/l vs 401.1 ± 143.5 nmol/l, $P=0.019$), while ACTH didn't show any difference (29.0 ± 21.9 ng/ml vs 23.8 ± 14.0, $P=0.236$). After $Dex_{0.5mg}$ there was no significant difference in cortisol suppression ($86.8\pm16.2\%$ vs $86.5\pm16.9\%$, $P=0.931$) in contrast to Dex_{1mg} where PCOS showed significantly better cortisol suppression ($94.9\pm2.4\%$ vs $92.7\pm5.8\%$, $P=0.020$). During dexametasone tests, HPA axis showed higher level of functionality in PCOS group in comparison to CG ($Dex_{0.5mg}$: $F_{1,98}=5.97$, $P=0.016$; Dex_{1mg}: $F_{1,98}=4.88$, $P=0.029$).
Conclusion
Women with PCOS have the same body composition and insulin resistance, but at the same time higher level of HPA axis functionality and better HPA axis sensitivity in comparison to respective controls. HPA axis hyperactivity in PCOS could be possible link towards cardiometabolic and psychological outcomes of the syndrome.

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Neuroendocrinology

GP138

Hypermethylation of tumour suppressor genes in pituitary adenomas: contribution to oncogenesis and tumour behaviour

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Introduction
Epigenetic and genetic alterations contribute to cancer initiation and progression. These alterations may be playing a determinant role in the development of pituitary adenomas (PAs). One of these epigenetic processes is the DNA methylation and, specifically, methylation of Tumour Suppressor Genes (TSG). TSG are key elements that allow the maintenance of cellular homeostasis. Due to epigenetic changes are reversible, a better understanding of the underlying epigenetic alterations during tumourogenesis and the discovery of epigenetic biomarkers are essential aspects to develop new therapies in these tumours. The aim of the present study was to analyse the methylation status of 36 TSG in a series of 105 PAs using the MS-MLPA technique and quantify the gene expression of methylated genes by qRT-PCR.
Methods
The study was performed in 105 PAs (35 silent gonadotroph adenomas (SGT), 15 silent corticotroph adenomas (SCT), 15 functioning corticotroph adenomas (CT) and 40 functioning somatotroph adenomas (ST)). Clinical, pathological, and radiological data were collected anonymously for each sample from the Spanish Molecular Registry of Pituitary Adenomas (REMAH) database. Tumours were classified as aggressive (invasive or ki67$\geq$3%) or non-aggressive (non-invasive and ki67$<$3%). MS-MLPA was used to analyse the promoter TSG hypermethylation. Gene expression was performed by qRT-PCR.
Results
Between the 36 TSG studied we chose the five genes with higher frequency of methylation in the overall series and in the different subtypes: *TP73*, *CADM1*, *CASP8*, *MGMT* and *RASSF1*. The expression of *CADM1* was significant lower in SCT and in CT than in SGT ($P=0.018$ and $P<0.001$, respectively). Moreover, the expression of CADM1 was also lower in CT than in ST ($P<0.001$). The expression of *RASSF1* was lower in ST than in SGT ($P=0.014$). There were no differences between subtypes in the expression of the other genes studied. *TP73* was the only TSG studied whose expression correlated negatively with the aggressiveness of PAs although only in SCT subtype ($P=0.037$). Regrettably, methylation was associated with a decrease in the expression of *TP73* only in the global series ($P=0.049$) but not in the SCT subtype.
Conclusions
In this series, we identified for the first time a reduction in the expression of *CADM1* in the pituitary tumours derived from Tpit lineage, a subset of PAs known by its special aggressiveness compared with other subtypes. Although a larger number of SCT should be studied, it is possible that the methylation of *TP73* could also contribute to the aggressiveness of this subtype of PAs.

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GP139

Why don't corticotroph tumours always produce Cushing disease?

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Introduction
Silent corticotroph tumours (SCT) are a pituitary tumours (PT) subtype of corticotroph lineage that do not clinically express Cushing disease. Inmunohistochemical (IHC) studies reveal no differences between SCT and functioning corticotroph tumours with Cushing Syndrome (FCT). However, the silencing mechanisms of this type of tumours are not fully understood.
Aim
In an important series of SCT, to sequence the *POMC* gene and quantify the expression of transcription factors of corticotroph lineage (*TBX19* (Tpit), *NEUROD1*) and convertases involved in the processing of *POMC* (*PC1/3*) and in the degradation of ACTH (*PC2, CPE* and *PAM*).
Material and methods
From our collection of 248 PT we chose 22 SCT, 22 FCT and 26 silent gonadotroph tumours (SGT) (control group). All the adenomas had previously been IHC and molecularly characterized. The molecular identification of SCT was based on an overexpression of *POMC, AVPR1b* and *CRHR1* genes similar to FCT and significantly higher than other subtypes of PT. The molecular study allowed to identify a subtype of SCT IHC negative for ACTH (IHC-ACTH(−)). The gene expression of *TBX19, NEUROD1, PC1/3, PC2, CPE* and *PAM* was studied by qRT-PCR with TaqMan probes. Moreover, in 18/22 SCT we performed a Sanger sequencing of the *POMC* gene.
Results
Preliminary sequencing of *POMC* in SCT identified some SNPs that are associated with *POMC* deficiency. Besides, compared with FCT, SCT showed an overall lower expression of *PC1/3* ($P=0.031$), only significant in microadenomas ($P=0.05$) but not in the FCT macroadenomas. There were no differences in the expression of the other genes studied. Molecularly identified IHC-ACTH (+) SCTs showed a higher *PC2* and *CPE* gene expression than IHC-ACTH (−) ones ($P=0.042$ and $P=0.052$, respectively). There were no differences in the expression of the other genes studied. Moreover, and in comparison to FCT, there were no differences in the expression of *PC1/3* and *PAM* between SCT and the control group of GT.
Conclusions
SCT have lower *POMC* expression and processing than FCT, especially in functioning microadenomas, while ACTH degradation is similar in both subtypes. Indeed, the expression of the genes involved in the degradation of ACTH seems to be related to the amount of this hormone in the tumour. Moreover, SCT share some similarity with SGT in the processing of *POMC* and in the degradation of ACTH, suggesting the possible existence of silent corticogonadotroph tumours.

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GP140

New horizons in medical treatment of Bronchial Carcinoids: evidence from *in vitro* models

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Introduction
Bronchial Carcinoids are rare neoplasms originating from the diffuse neuroendrocrine system. Surgery is the only effective therapy but may not be feasible due to metastases. Available therapy may control symptoms but not tumor bulk. Everolimus has shown promising results, however patients may develop resistance. Previous studies demonstrated that Everolimus reduces viability of NCI-H720 (Atypical Carcinoid) but not of NCI-H727 cells (Typical Carcinoid). In order to find molecular targets different from mTOR, we previously assessed CDKs and cyclins protein levels in both NCI-H720 and NCI-H727 cells and found a differential expression pattern.
Aim
This study is aimed to test the efficacy of a CDK inhibitor, Dinaciclib, alone and in combination with Everolimus on NCI-H720 and NCI-H727 cells. We also investigated the involvement of autophagy in mediating the effects of Dinaciclib on cell viability and LC3B expression (autophagosome protein) by using a well-established autophagy inhibitor, Chloroquine.
Methods
Cell viability was tested by a luminescent assay and protein levels by Western blot analysis.
Results
Treatment with Everolimus (100 nM) reduced viability in NCI-H720 (−26% vs control; $P<0.01$) and in NCI-H727 cells (−19% vs control; $P<0.01$). Dinaciclib (100 nM) significantly reduced viability in both NCI-H720 (−39% vs control; $P<0.01$) and NCI-H727 cells (−62% vs control; $P<0.01$). Dinaciclib potentiated the inhibitory affects of Everolimus on NCI-H720 viability (−24% vs Everolimus; $P<0.01$), while in NCI-H727 cells the combination did not modify the inhibitory effects of Dinaciclib. Co-treatment with Chloroquine 1 mM did not modify these results. In addition, we assessed autophagosome protein LC3B by Western blot analysis. We found that LC3B levels were not influenced by the employed drugs in NCI-H727 cells. In NCI-H720 Dinaciclib reduced LC3B levels independently of the combination with Everolimus (−37% and −48% respectively vs. control); Everolimus alone did not influence LC3B levels. Chloroquine determined a reduction in LC3B levels (−40% vs control), and this effect was not influenced by Everolimus. On the contrary, Dinaciclib potentiated Chloroquine effects on LC3B reduction (−44.5% vs Chloroquine) independently of the combination with Everolimus.
Conclusions
Our results indicate that Everolimus effects are not mediated by autophagy. On the contrary, Dinaciclib inhibits autophagy in NCI-H720 but not in NCI-H727, indicating that in the latter cells the antiproliferative effects of Dinaciclib are mediated by mechanisms different from autophagy. At the same time, Dinaciclib could represent a good candidate for medical treatment of Bronchial Carcinoids, especially for those patients resistant to Everolimus.

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GP141

Reproductive and metabolic consequences of AMP-Activated Protein Kinase (AMPK) ablation in GnRH neurons

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GnRH neurons are the final output of the brain controlling reproduction. These neurons receive information from multiple central and peripheral signals, ranging from gonadal steroids to metabolic cues and brain neuropeptides, to regulate their activity. AMP-activated protein kinase (AMPK) is an intracellular sensor, activated by energy deficiency, involved in the regulation of the cellular and whole-body energy homeostasis. Previous *in vitro* studies suggested the participation of AMPK in the negative regulation of GnRH neuronal excitability in response to glucose deprivation. Nonetheless, the physiological relevance of AMPK signaling in GnRH neurons for the metabolic control of the reproductive function remains unknown. In this work, we aimed to explore the roles of AMPK signaling in GnRH neurons by generating a transgenic mouse, named GAMKO, with congenital elimination of the catalytic AMPK alpha-1 subunit specifically in this neuronal population. Ablation of AMPK in GnRH neurons resulted in advanced puberty onset in female, but not male mice. Moreover, acyclic GAMKO females, due to chronic caloric restriction, had a faster recovery of the estrous cyclicity after re-feeding, compared to control mice. Both features are compatible with unrestrained GnRH secretion in the absence of AMPK, which would drive a negative valence when become active (e.g., in conditions of negative energy balance). In addition, GAMKO females showed enhanced responsiveness to GnRH administration, in terms of LH secretion. On the other hand, adult GAMKO mice had increased fat mass and body weight, being already evident in

males at the time of puberty. All in all, our data are the first in describing the potential role of AMPK in GnRH neurons for the regulation of reproduction and metabolism. Further characterization of the reproductive (LH pulsatility, ovarian histology) and metabolic (insulin resistance, energy consumption) phenotype of GAMKO mice is currently ongoing in order to fully disclose the physiological function of this key energy sensor in the dynamic regulation of GnRH neurons and the bodily functions controlled thereby.

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GP142

Preoperative SSA treatment positively affects the outcome of pituitary neurosurgery in acromegaly patients

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Introduction
Treatment with somatostatin analogues (SSA) leads to shrinkage of pituitary adenoma in acromegaly naïve patients, as shown by the PRIMARYS study. Therefore the effect of this treatment on surgery was investigated.
Aim
To evaluate the efficacy of pre-treatment with SSA in acromegaly patients qualified for neurosurgery.
Material and methods
Group A (46 patients: 36 female, 10 male) were pre-treated with SSA. Group B (49 patients: 30 female, 19 male) were not treated, their mean ages at diagnosis: 49.2 ± 13.9 years and 41.2 yrs ± 13.1, respectively ($P = 0.005$). Group A- patients were treated with SSA (octreotide 30 mg and lanreotide autogel 120 mg every 4 weeks) for 3–6 months before surgery.The percentage of microadenomas/ macroadenomas in group A and group B was 21.7/78.3% and 6.3/93.7%, respectively ($P = 0.026$).
Results
In groups A and B, GH concentration at 120 min in OGTT and IGF-1 ULN concentration before surgery did not differ. Median values of IGF-1 before surgery in groups A and B were 748.0 (range 113.0–1872.9) ng/ml and 1026.5 (447.0–1998.9) ng/ml, respectively, $P = 0.031$. Three months after surgery, significant difference of median GH concentrations at 120 min was observed between group A: 0.58 (0.20–24.30) ng/ml and group B: 1.10 (0.15–58.40) ng/ml, $P = 0.035$, as well as between median of IGF-1 concentrations: group A: 240.5 (62-912) ng/ml and group: B 352.4 (88–1150) ng/ml, $P = 0.05$. In group A 73.3% of patients were considered cured, and 26.7% required further SSA treatment. In group B 32.6% of patients were considered cured, and 67.4% required further SSA treatment, $P = 0.0001$.Of those patients who required further SSA treatment 75% in group A and 64.5% in group B were well controlled. According to our most recent evaluation, in group A the levels of GH, IGF-1and ULN were: 1.57 (0.35–10.00) ng/m; 174.5 (51–558) ng/ml and 0.48 (0.16–1.87), respectively, while these levels in group B were: 1.40 (0.20–7.70) ng/ml; 226.5 (79-559) ng/ml and 0.60 (0.25-2.73), respectively. Only the difference in IGF-1 levels between groups A and B was statistically significant, $P = 0.0489$.Following multi-dimentional step-wise regression, pituitary microadenoma, IGF-1ULN after surgery, and SSA pre-treatment, were positive predictors of the final outcome, with respective odds ratios: 32.02 (±95% CL 2.17–472.0, $P = 0.0104$), 0.11 (± 95% CL 0.02–0.53, $P = 0.0054$) and 34.97 (±95% CL 7.63-160.38, $P = 0.0000$).
Conclusion
SSA pre-treatment improves the final outcome of pituitary surgery in acromegaly patients.

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GP143

Characterization and functional rescue of a nephrogenic diabetes insipidus causing S127F substitution in V2 vasopressin receptor

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The concentrating function of the kidney is important to maintain the water homeostasis of the body. It is regulated by the arginine-vasopressin system through the type 2 vasopressin receptor (V2R). Loss-of-function mutations of V2R in kidney can lead to nephrogenic diabetes insipidus (NDI) which results several symptoms such as polyuria, polydipsia, and hyposthenuria. In this study, we functionally characterized and investigated the potential rescue of a missense mutation (S127F) of the V2R. We monitored the cellular localization of the S127F mutant V2 receptor using HA-tagged receptors in confocal microscopy experiments. The S127F V2 receptor was detected only in the endoplasmic reticulum but not in the plasma membrane. We also measured the cAMP signaling capability of the mutant receptor with BRET measurements. The S127F receptor was not able to increase the intracellular cAMP levels in response to vasopressin stimulation. Certain ER retention mutations can be rescued by pharmacological chaperones, which cause misfolded mutant receptors to present in the plasma membrane. We examined the effect of tolvaptan (a V2R antagonist) on the S127F V2 receptor. HEK293 cells were transiently transfected with the plasmid of the mutant receptor and after one day the cells were incubated for 18 h with tolvaptan. After the pretreatment, the cells were exposed to vasopressin, and we were able to detect significant cAMP signal generation of the mutant receptor. We also checked whether the result after tolvaptan pretreatment was due to restored plasma membrane location of the receptor. We were able to demonstrate significant increase of the mutant receptors in the plasma membrane using flow cytometry. We also investigated the effect of pharmacochaperone MCF14 compound (a cell permeable high-affinity agonist for the V2R) on the mutant receptor and we found that the MCF14 was also capable to restore the cAMP signaling function of the receptor. According to our data, pharmacochaperones could be the treatment for patients carrying the S127F mutation.
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GP144

Genetics of binge-eating disorder (BED): a pilot study

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Binge-eating disorder (BED) is characterized by recurrent (≥1 per week for 3 months), brief (≤2 h), psychologically distressing binge-eating episodes during which patients sense a lack of control and consume larger amounts of food than most people would under similar circumstances. The prevalence of BED is estimated to be between 2% and 3.5% and majority of individuals with BED are either overweight or obese. Most of the genetic research about eating disorders (ED) has focused on Anorexia Nervosa and Bulimia Nervosa; less data are available for BED due to its status as a newly recognized ED diagnosis. Although family and twin studies suggest the role of genetic factors in BED, candidate gene studies have not clearly confirmed the involvement of any one gene or genetic pathway. The aim of our study was to examine the existence of genetic variants associated with the onset of BED, using the Next-Generation (NGS) technology. We analyzed 42 genes involved in neuro-regulation of hunger/satiety associated with BMI and/or obesity and/or eating disorders in 50 obese patients (BMI $>40\ kg/m^2$) affected by BED and in a control population (72 normal weight subjects overlapping with our cases by sex and age without a diagnosis of eating disorders). Twenty-eight obese patients with BED are mutated in 19 of the genes analyzed; of these, 12% vs 4% of controls carries more than one variant in different genes. Within the control population, fewer mutations were found (33%) compared to the case population, in which the percentage of the changes (56%) was higher than the percentage of the Wild-Type (44%). These differences indicate a statistically significant enrichment of rare variants in BED patients compared to controls according to the Exact Fisher Test ($P = 0.0159$). Several genes tested positive are known to be involved in the reward system and in the hedonic hunger (FTO, OPRM1, GHRL and LEPR), but we discovered new loci with a novel possible involvement in hedonic hunger. To date, our study is the first NGS study in a series of obese patients with BED and suggests for the first time some mechanisms potentially involved in conferring a genetic susceptibility to development of a BED.

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GP145

Hyponatremia-associated mortality and volemia in patients on parenteral nutrition: a prospective multicenter study

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Introduction
In patients receiving Parenteral Nutritcion (PN), hyponatremia is associated with increased in-hospital mortality. Our objective was to evaluate the influence of volemic classification (hypovolemia, euvolemia or hypervolemia) on in-hospital mortality in patients receiving PN presenting hyponatremia.
Methods
Prospective, non-interventional, multicenter study in 19 Spanish hospitals. 543 non-critical patients receiving PN were recruited. Hyponatremia was defined as a Serum sodium level (SNa) $<$ 135 mmol/l. Patient data collected included gender, age, prior comorbidity, body mass index-BMI-, nutritional assessment by subjective global assessment (SGA), SNa at start of and during PN, in-hospital mortality, and type (volemic classification) of hyponatremia. Duration of PN, metabolic and infectious complications related to PN were also registered. Statistics: univariate and multivariate logistic regression.
Results
60.2% were men. Median age 67 [IQR 57–76]. 162 patients (29.8%) presented hyponatremia. Clinical volemia was evaluated in 137/162: 14.6% were hypovolemic, 67.9% euvolemic, 17.5% hypervolemic. In-hospital mortality was: 13.6% (22.5% of hyponatremic patients vs 9.8% of normonatremic patients; $P<0.001$). In-hospital mortality according to hyponatremia type was: 20.0% in hypovolemic patients, 20.9% in euvolemic patients, 41.7% in hypervolemic patients ($P=0.096$). In multivariate logistic regression, hyponatremia was independently associated with increased in-hospital mortality (OR 1.83 [95% CI 1.03–3.24]; $P=0.039$), following correction for age, gender, SGA, BMI, prior comorbidity, duration of PN and metabolic /infectious complications related to PN. In the same multivariate analysis model, the Odds Ratios for in-hospital mortality by type of hyponatremia as compared with patients with eunatremia were: 1.95 (95% CI 0.54–7.07, $P=0.307$) in hypovolemia, 1.44 (95% CI 0.69–3.00, $P=0.337$) in euvolemia, and 3.36 (95% CI 1.17–9.63, $P=0.024$) in hypervolemia.
Conclusion
Hyponatremia is independently associated with increased in-hospital mortality in patients receiving parenteral nutrition. Patients with hypervolemic hyponatremia present a marked increase in mortality risk as compared with patients presenting eunatremia.

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GP146

Hyperglycemia causes a reduction in FSH levels following aberrant epigenetic regulation in the gonadotropes due to the increased glucose metabolism

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The connection between metabolic state and fertility is well-recognized, and the hypothalamus clearly plays a central role in translating metabolic signals into altered GnRH release which affects the reproductive axis. We hypothesized that the gonadotropes might also directly impart some of the effects of hyperglycemia on reproductive function. Gonadotropes were shown to express predominantly the insulin-independent Glut-1 transporter, and their incubation in high glucose increases expression of the glucose responsive *Txnip* gene while altering levels of various glucose metabolites. The drop in NAD+ and increase in α-ketoglutarate affect the activity of Sirtuin histone deacetylases, JmjD histone demethylases and Tet DNA hydroxymethylases/demethylases, all of which use these metabolites as cofactors. Accordingly, gonadotropes in high glucose showed elevated histone acetylation and H3K4 trimethylation, reduced DNA methylation and increased hydroxymethylation, all of which are associated with elevated gene expression. Transcriptome analysis revealed that expression of many genes increased after incubation in high glucose. Notably however, *Fshb* expression was repressed in high glucose conditions, both in cultured cells and in two hyperglycemic mouse models *in vivo*. In one of these, circulating FSH levels were also significantly reduced. Increased expression and secretion of inhibin appears partly responsible for this repressive effect on *Fshb*. Although return of cells to normal glucose restored expression of some of the genes, *Fshb* levels remained low and the affected chromatin modification were not reversed. Our findings suggest that hyperglycemia aberrantly affects the gonadotrope epigenome with potentially long-term effects on gene expression and thus also reproductive function.

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GP147

Macrophages involvement in neuroendocrine tumor behaviour and progression

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Neuroendocrine tumors (NETs) are rare neoplasms showing a wide spectrum of clinical behaviors. The therapeutic options available for NET treatment are rarely curative and most are palliative, as NETs frequently show resistance to pharmacological therapy. Cancers develop in complex tissue environments, which they depend upon for sustained growth, invasion and metastasis. A major characteristic of the tumor microenvironment is inflammatory cell infiltration, where tumor-associated macrophages (TAMs) are a major cellular component. The polarized state of macrophages is classified into two subsets: classically activated M1 (anti-tumor promoting effects) and alternatively activated M2 (pro-tumor promoting effects). Thus the restoration of an M1 phenotype may provide therapeutic value by promoting anti-tumor behavior. The importance of immune microenvironment and the role of macrophages in NET are poorly understood. Aims of the study are: to investigate the effects of the different macrophages subtypes (M1, M2) on biological behavior of primary NET cells and QGP1 (pancreatic-NET) and H727 (pulmonary-NET) cell lines. We found that M1 macrophages significantly decreased the viability of QGP1 cell line ($-40\pm14\%$ $P<0.01$ vs basal) and H727 cell line (-43 ± 8 $P<0.01$ vs basal). Moreover, CM (conditioned medium) of M1 macrophages strongly decreased colony formation, colony average area and cell number (QGP1: $-42\pm17\%$ $P<0.05$ vs basal; H727: $-60\pm15\%$ $P<0{,}001$ vs basal) after 7 days of incubation. As shown by flow cytometry analysis, after CM of M1 macrophages treatment, G0/G1 phase was increased in H727 cells ($+18\pm7\%$ $P<0.05$), whereas G2/M phase was decreased in QGP1 cell ($-44\pm4\%$ $P<0.05$). Interestingly, as shown by real time analysis, the CM of NET cell lines promoted the differentiation of macrophages into an M2 phenotype, after 24 h of culture. Moreover, as shown in preliminary data of primary pancreatic NET cells, CM of M1 macrophages strongly decreased cell proliferation, whereas CM of M2 macrophages promoted it. In conclusion, M1 macrophages have a potent anti-tumor effect, able to affect the proliferation and the tumorigenicity of NET cell lines. Interestingly, NET cell lines contribute to promote a M2 phenotype of macrophages, suggesting a potential involvement of tumor microenvironment in the behaviour of pulmonary and pancreatic NETs.

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GP148

Mountain cycling ultramarathon effects on neuromuscular, immune and stress biomarkers

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Introduction
The long-term mountain cycling effects on cognitive development for better performance, are still not fully elucidated. Notwithstanding, this type of exercise may induce a link with energy metabolism and sympathetic nervous system. We previously observed that a mountain cycling ultramarathon, induced a comodulatory influence of genetic- and exercise-associated factors on inflammatory and haemoglobin catabolic marker haptoglobin. We hypothesised that inflammatory process may induce hypothalamic-pituitary-adrenal (HPA) activation with consequent neuromuscular functional changes in long-term mountain cycling.
Methods
Fifty-five non-professional athletes (mean age 44.8 ± 7.1 years) participating in a 9-day mountain cycling ultramarathon (TransPortugal) were evaluated. Before and immediately after race were determined the following parameters: insulin, glucose, uric acid, creatinine and platelets by standard methods; IL-6-plasma, BDNF-serum, cortisol-salivary and irisin-serum by ELISAs. Δ% represents values adjusted for plasma volume. Body composition was evaluated by BIA-Quantum-X. Participants were also categorized according to the number of courses completed (<9 or 9 courses).
Results
After race, IL-6 and platelets increased by 1129.7% ($P<0.0001$) and 13.3% ($P<0.0001$), respectively, while BDNF and cortisol levels didn't change ($P>0.05$). At post-race, BDNF was directly correlated with % fat mass ($r=0.286$, $P<0.05$), glucose ($r=0.294$, $P<0.05$), platelets ($r=0.462$, $P<0.01$) and inversely correlated with skeletal muscle mass (kg) ($r=-0.469$, $P<0.01$). Post-race IL-6 was directly correlated with Δ% uric acid ($r=0.341$, $P<0.01$), Δ% insulin ($P=0.287$, $P<0.05$), Δ% HOMA-IR ($r=0.289$, $P<0.05$), Δ% HOMA- β ($r=0.315$, $P<0.05$) and post-race cortisol ($r=0.368$, $P<0.01$). The Δ% cortisol was directly correlated with Δ% creatinine ($r=0.319$, $P<0.05$), Δ% uric acid ($r=0.439$, $P<0.01$), Δ% glucose ($r=0.332$, $P<0.05$), Δ% insulin ($r=0.293$, $P<0.05$) and Δ% HOMA-IR ($r=0.373$, $P<0.05$). The completers of 9 courses, presented higher values of the Δ% IL-6 ($P=0.043$), Δ% cortisol ($P=0.008$), and post-race BDNF levels ($P=0.053$). Only for completers, the fastest (≤3715 min) presented lower values of BDNF in relation to the athletes of intermediate group (3715–4030 min) ($P=0.013$). Irisin levels were lower for athlets with better performance/fastest ($P=0.033$).
Conclusion
The HPA-axis hyperactivity may decrease BDNF production via IL-6 inflammatory response activation. The increased BDNF levels for 9 courses completers could reflect an management capacity, throughout multiple mediators of HPA axis, autonomic nervous system, and components of the immune system. Cerebral blood flow may decrease during very high intensity exercise, compromising the production of BDNF and, as such, consumption of foods rich in nitric oxide precursors may improve the flow, decreasing the inflammatory process.

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Obesity

GP149

Sex hormone-binding globulin is more than a sex steroid carrier: a New therapeutic target against obesity and non-alcoholic fatty liver disease

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Low plasma SHBG levels are present in patients suffering chronic metabolic diseases, including obesity and non-alcoholic fatty liver disease (NAFLD). In overweight individuals, low plasma SHBG levels are a biomarker for the metabolic syndrome and predict a higher risk of suffering type 2 diabetes and cardiovascular disease. Our recent results demonstrate that SHBG is more than sex hormone carrier and its reduction in obese subjects play an active role in obesity and NAFLD development independently of sex steroids. We have demonstrated these new SHBG actions using different approaches including an *in vitro* approach, developing different transgenic mouse models and using human samples. Regarding the *in vitro* approach, we have used HepG2 cells underexpressing and overexpressing SHBG. We have developed a genetically-induced model of obesity and expressing human SHBG (crossing human *SHBG* transgenic mouse with C57BL/ksJ-db/db mouse), a diet-induced NAFLD model (by feeding human *SHBG* transgenic mice and their wild-type littermates with high fructose diet (HFrD) during 8 weeks and a diet-induced obesity model by feeding human *SHBG* transgenic mice and their wild-type littermates with high fat diet (HFD) during 8 weeks. We have elucidated the molecular mechanisms associated by which SHBG protected against NAFLD development and HFD-induced obesity. Moreover, human liver biopsies were used to corroborate the *in vivo* and *in vitro* findings. Overall, our results point out to SHBG as a protective factor against obesity and NAFLD. Therefore, SHBG could be a new therapeutic target whereby increased expression may reduce obesity and NAFLD.

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GP150

Use of ultrasonography as a simple diagnostic method to measure different abdominal fat layers and metabolic syndromeprediction

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Introduction
Waist circumference is a validated tool to measure obesity-associated cardiovascular risk factor. However it does not differentiate between superficial and visceral abdominal fat. Ultrasonography has many advantages over TC/DEXA in abdominal fat assessment, specially imaging pre-peritoneal, omental and retroperitoneal fat. Our aims were to validate the diagnostic technique and to observe correlations between different abdominal fat layers with clinical and analytical parameters related to obesity comorbidities.
Methods
$n=274$ patients, mean age 53, 82 (30%) males, 192 (70%) females (59% menopause), mean BMI 31 kg/m^2 (19.2% normal weight, 28,8% overweight, 52.2% Obesity), came for conventional abdominal US. Thickness of 6 different consecutive layers of abdominal fat at the L4 level were assessed using a 12 MHz linear and 3–6 MHz convex probes (GE logic E): Superficial and deep subcutaneous fat; Pre-peritoneal fat; Peri-aortic (omental) fat; Hepatic steatosis area (cm^2) and hepatic US noise (dB) (visceral fat); Pre-renal fat (Left and Right) (retroperitoneal fat). We also obtain: Waist circumference (WC), Glucose, insulinaemia, HOMA index, leptin, Total cholesterol, LDL, HDL, Triglycerides, DM2 diagnosis, Hypothyroidism and Metabolic Syndrome according to ATPIII criteria.
Results
We found a different sex distribution pattern at the SC (mean range 23.28 mm F and 20.16 mm M), pre-peritoneal (10.47 mm F and 11.34 mm M) and peri-aortic fat layers (44.33 mm F and 66.63 mm M) ($P<0.05$). Only peri-aortic fat correlates with BMI ($r=0.446$; $P<0.001$) and WC ($r=0.456$; $P<0.001$). Peri-aortic, Right pre-renal, but specially Pre-peritoneal fat ($P<0.001$, CI 8–20 mm) correlate with steatohepatitis. Menopause predisposes to greater peri-aortic fat ($P<0.001$, CI 6–18 mm) as well as Metabolic Syndrome ($P<0.001$, IC 16–27 mm). In a multi-variant analysis, only peri-aortic fat layer thickness and Waist Circumference may predict metabolic syndrome. Peri-aortic fat >34.5 mm in F (AUC=0.761; $P<0,001$; 74% sensibility and 60% specificity) and >56.5 mm in M (AUC=0.763; $P<0,03$; 75% S and 70% E), are predictive for metabolic syndrome (ROC curves).
Conclusions
US is an easy method for the stratification of different abdominal fat layers. More than global visceral fat, US highlights the clinical importance of strict peri-aortic (omental) fat layer, with good correlations with BMI, WC and steatohepatitis. We suggest a cut-off point of 34 mm in F and 56 mm in M to consider the thickness of the omental layer as pathological and predictive of metabolic comorbidities. Pre-peritoneal fat thickness with a linear probe may also be an easy way to estimate Steatohepatitis.

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GP151

Improvement in insulin-mediated suppression of branched-chain amino acid flux is responsible for the post-bariatric surgery decrease in plasma branched-chain amino acid levels

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Background
Branched-chain amino acids (BCAA) are elevated in morbid obesity and decreases significantly following bariatric surgery. This decrease is associated with the post-surgical improvement in insulin resistance (IR) and may be secondary to the reduction in BCAA flux from proteolysis or an increase in BCAA catabolism. Presently, the underlying mechanism is unclear.
Aim
To investigate the changes in BCAA metabolism in morbidly obese individuals following bariatric surgery.
Hypothesis
The decrease in plasma BCAA after bariatric surgery is due to the improved ability of insulin to suppress BCAA flux from proteolysis.
Methods
11 morbidly obese non-diabetic subjects scheduled for sleeve gastrectomy and 9 healthy non-obese controls were recruited. Metabolic assessments were performed for all subjects at baseline and at 6 months for the surgical subjects. IR was quantified as the insulin sensitivity index (ISI) obtained using the hyperinsulinemic-euglycemic clamp method and plasma BCAA and short-chain acyl-carnitines (ACs) were measured using mass spectrometry during fasting and insulin clamp.
Results
Morbidly obese subjects were significantly more insulin resistant than controls at baseline with a lower ISI (4.39 ± 1.95 vs 17.27 ± 7.31 mg/kgFFM per min per μU/ml·100). Following surgery, there were significant reductions in weight (114.80 ± 22.64 to 91.90 ± 16.65 kg), BMI (39.09 ± 4.68 to 31.29 ± 2.91 kg/m^2) and increase in ISI (4.39 ± 1.95 to 13.68 ± 3.36 mg/kgFFM per min per μU/ml·100). Plasma BCAA in morbidly obese subjects were similar to controls during fasting, but decreased to a greater extent in the control group following insulin infusion such that BCAA levels measured during the insulin clamp were significantly higher in the morbidly obese (332.47 ± 88.77 vs 235.32 ± 33.00 μM). However, no difference in short-chain ACs between the two groups was found. Interestingly, plasma BCAA during fasting and insulin clamp both decreased significantly (fasting BCAA 445.37 ± 75.21 to 326.19 ± 54.88 μM; insulin clamp BCAA 332.47 ± 88.77 to 211.56 ± 44.16 μM) following bariatric surgery but also without any changes in short-chain ACs levels.
Conclusion
The impaired ability of insulin to suppress BCAA flux is responsible for the higher plasma BCAA level in morbidly obese individuals during insulin clamp at baseline while the decrease in BCAA following bariatric surgery can be attributed to the improvement in insulin-mediated suppression of branched-chain amino acid flux. BCAA catabolism by contrast did not play an important role.

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GP152

Cell-derived extracellular vesicles as important intercellular messengers in obesity

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Introduction
Extracellular vesicles (EVs) are submicron vesicles released by most cells. They contain protein, enzymes and microRNA of the donor cells and are believed to play a role in paracrine communication. Circulating EVs might reflect heightened immune/inflammatory status in obese individuals and play a role in initiation/modulation of chronic low grade inflammation associated with obesity.
Aims
To compare circulating plasma EVs between healthy volunteers and morbidly obese individuals attending a multidisciplinary weight loss clinic, and to assess the effects of lifestyle changes on the circulating EV profile.
Methods
EVs were isolated by differential centrifugation and measured by Nanoparticle Tracking Analysis (NTA). EV cellular origin (platelets CD41, monocytes/macrophages CD11b, erythrocytes CD235a, endothelial cells CD144) and adipocytokine expression (IL6, TNFα, interferon γ, adiponectin, FABP4, PPARγ) were evaluated by TRF immunoassay.
Results
Circulating EV profile and concentration in metabolically healthy volunteers was unaffected by BMI (all P=ns). However, the EV profile in healthy men appears to be more pro-inflammatory compared to women, with higher EV-expressed CD41, CD144, EV-IL6, interferon γ and FABP4 (all $P<0.05$). This was also reflected by lower plasma adiponectin concentration in males (128 μg/ml vs 272.3 μg/ml, $P<0.005$). Plasma FABP4 correlated strongly with BMI ($r=0.91$, $P<0.005$) and was lower in healthy lean versus obese individuals (13.5(6.4) vs 23.8(6.4) ng/ml, respectively ($P<0.05$)) despite fasting glucose and HOMA-IR being within the normal range (P=ns). Dietary and lifestyle management affected the EV profile, with lower signals observed from platelet- and endothelial cell-derived EVs ($P<0.05$) as well as FABP4-, TNFα- and Interferon γ-expressing EVs at 6 months' follow-up ($P<0.05$, $P=0.05$, $P=0.06$, respectively). The exosomal marker CD9 correlated with FABP4, interferon γ, adiponectin and TNFα ($r=0.49$, $r=0.41$, $r=0.59$, $r=0.53$, all $P<0.05$), suggesting that exosomes are the main carrier of these adipokines.
Conclusion
EVs can be regarded as diverse biological vectors playing an important role in regulation of adipose tissue homeostasis and inflammatory processes. Their concentration, cellular origin and content do not directly correlate with BMI but are affected by gender and the presence of obesity-driven comorbidities.

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GP153

How to better predict weight loss and type 2 diabetes remission after bariatric surgery? the potential role of genetic scoring systems in clinical practice

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Introduction
Obesity and its comorbidities, specially type 2 diabetes (T2D), are a major public health problem. The disappointing result of dietary treatment and the scarce of drugs have led to increased bariatric surgery (BS) as the most efficient therapeutic option. However, not all obese patients with T2D who undergo BS achieve diabetes remission.
Objective
To develop a genetic scoring system for predicting T2D remission following BS. 2) To compare our results with the current clinical based prediction score (DiaRem).
Material and methods
We used a retrospective Spanish cohort (n=820) that included 169 individuals with T2D followed at least 18 months after BS (109 gastric bypass and 60 sleeve gastrectomy). DNA was extracted from saliva samples and processed using Nutri inCode test (NiC, Ferrer inCode) based on 6 genetic predisposition risk scores (GPS). Each GPS consists of several SNPs which were shown to be implicated in

appetite regulation, response to exercise, response to hypocaloric diet, response to lyfe style intervention, response to BS, and SNPs related to the presence of metabolic syndrome or T2D. Multivariate logistic regression was used for adding several GPS to DiaRem score creating new scores, to predicting the event of interest (T2D remission). The calibration of the adequacy of the different models was determined by Hosmer-Lemeshow test and the area under the receiver operating characteristic curve (AUC) was used for evaluating the prediction performance for each score.
Results
In patients underwent BS, the genetic test significantly predicted not only an excess weight loss higher than 50% [gastric bypass: 0.610 (0.503–0.717), $P=0.044$; sleeve gastrectomy: 0.693 (0.594–0.791), $P<0.001$)] but also T2D remission. In addition, this new test improved the AUC compared with DiaRem alone in patients underwent gastric bypass [0.816 (0.701–0.932) vs 0.718 (0.576–0.861), $P=0.024$] and sleeve gastrectomy gastrectomy [0.816 (95% IC: 0.701–0.932) vs 0.718 (0.576–0.861), $P=0.024$]. Notably the GPS for diabetes remision were not the same that for weight loss.
Conclusion
To identify subjects with an inadequate response before BS is a challenge for all healthcare systems. Our results suggest that genetic testing is a useful tool for this issue and could be incorporated to the current clinical practice. Clinical data helps to better predict diabetes remission following BS.
Aknowledgement
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GP154

Eating and substance-related disorders after bariatric surgery
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Introduction
Obesity is a chronic condition with great morbidity, mortality and significant economic and psychosocial impact. Bariatric surgery has proven to be an effective therapy for sustained weight loss and has allowed a reduction in medical comorbidity and an improvement in self-esteem and life quality. However, recent evidence reports an increase in eating and substance-related disorders that are diagnosed in the postoperative period worsening the prognosis.
Objectives
To evaluate the development of eating and substance-related disorders in patients undergoing bariatric surgery.
Material and methods
A retrospective review of patients undergoing bariatric surgery was performed between January 2006 and December 2014 in our center. As per protocol, all the patients underwent a complete psychiatric and psychological evaluation before the surgery. Patients with previous mental disorders were excluded.
Results
Of 500 patients that underwent bariatric surgery in this period of time, 9 cases (4 women and 5 men) presented with new psychiatric disorders 3.67 ± 1.87 years after the surgery (1.8% of patients). The baseline characteristics of the patients were: age 41.89 ± 8.71 years, pre-surgery BMI 43.61 ± 6.82 kg/m^2. The patients underwent: Y-Roux gastric bypass (6), sleeve gastrectomy (2) and duodenum-ileal bypass over sleeve gastrectomy (1) and presented with BMI 31.20 ± 8.53 kg/m^2 after three years follow-up ($P<0.001$). A total of 66.67% developed eating disorders (6/9 patients): 1 case met criteria for restrictive food intake disorder, 2 for atypical anorexia nervosa, 1 for binge eating disorder, and the other 2 had problems in the self-control emotions and behaviors and anxiety disorders with a loss of control over feeding. The rest of patients 33.33% developed substance-related disorders (3/9 patients): 2 cases of alcohol and 1 of alcohol + cocaine use disorders. A weight regain 17.6 ± 7.44% during follow-up was seen in patients with binge eating disorders, problems in self-control or anxiety disorders and alcohol use disorder.
Conclusions
In our study, new mental disorders in the form of eating and substance-related disorders were higher than in general population (1.8% versus 1.01%) in patients without mental disorder before bariatric surgery. The development of eating and substance-related disorders influences the evolution of body weight after bariatric surgery. More studies are needed in order to evaluate the risk of new mental disorders in patients underwent bariatric surgery. A rigorous postoperative follow-up is needed to reinforce permanent changes with the new lifestyle, such as diet and exercise, and to detect abnormal behaviors.
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GP155

Changes in gut microbiota and metabolic profiles after sleeve gastrectomy
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We aimed to assess the effect of sleeve gastrectomy (SG) on the metabolic and gut microbiota profiles in non-diabetic obese patients with different grade of insulin resistance (IR).
Methods
Prospective study of 22 morbid non-diabetic obese patients (77.2% women, age 47.13 ± 9.51 years, basal BMI 45.59 ± 4.99 kg/m^2, 11 IR and 11 non-IR) undergoing SG. A fasting blood sample was collected at baseline and at 6 months post-SG for the determination of glycaemia, HbA1c, insulin, C-peptide, complete lipid profile. Gut microbiota study and body composition analysis by dual-energy X-ray absorptiometry (DEXA) were performed at the same time-points.
Results
At baseline insulin and C-peptide were higher in IR group (19.10 ± 4.47 vs 11.83 ± 4.80 m.u.int/l, $P=0.001$ and 3.59 ± 0.98 vs 2.33 ± 0.49 ng/ml, $P=0.016$, respectively) with no differences in lipid profile. At 6 months after SG, a significant decrease in BMI, waist circumference, blood pressure was observed, as well as a fat mass similar decrease in both groups, although fat free mass only decreased in non-IR group (52.17 ± 7.47 vs 46.86 ± 6.73 kg, $P=0.04$). After SG, in IR-group: Phylum and family diversity increased (0.7 ± 0.10 vs 0.79 ± 0.11 and 1.58 ± 0.39 vs 2.1 ± 0.18, $P<0.005$, respectively); bacteroidetes decreased (71.16 ± 9.43 vs 51.48 ± 17.4, $P>005$) and firmicutes increased (25.07 ± 10.3 vs 43.96 ± 19.09, $P>0.005$). Prevotellaceae diminished and odoribacteraceae rose ($P<0.05$). In non IR-group: family and genus richness decreased (186 ± 43.71 vs 159.4 ± 43.75, $P<0.005$ and 592 ± 187.03 vs 487 ± 171.01, $P<005$, respectively), Prevotellaceae diminished but not significantly (20.92 ± 30.09 vs 13.02 ± 21.69), and odoribacteraceae increased (0.63 ± 0.41 vs 2.32 ± 2.53, $P<0.005$) but there were no changes in bacteroidetes or firmicutes.
Conclusions
SG produces different effects on gut microbiota composition in non-diabetic patients with different grade of insulin resistance despite similar changes in BMI, waist circumference and fat mass. The decrease in Prevotellaceae and the increase in Odoribacteraceae after SG could be related with the enhancement of inflammation and metabolic dysfunction observed in patients undergoing bariatric surgery.
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GP156

Pharmacological stimulation of p53 with low-dose doxorubicin ameliorates diet-induced nonalcoholic steatosis and steatohepatitis
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Introduction
p53 is a transcription factor involved in many biological functions such as stress, ageing, and metabolism. Although there is a large body of evidence showing that p53 promotes fatty acid catabolism while it inhibits anabolism through the regulation of gene expression, the possible contribution of p53 to the pathogenesis of nonalcoholic fatty liver disease (NAFLD) remains to be elucidated. Also, the anthracycline doxorubicin is an important chemotherapeutic agent, which therapeutic actions depends on p53, since p53 mutations are associated with resistance to this drug.
Objective
We hypothesized that the pharmacological activation of p53 with low-dose doxorubicin may have beneficial effects on nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).
Methods
We used long-term pharmacological activation of p53 by intraperitoneal injection or oral administration of low-dose doxorubicin in different animal models of NAFLD (high fat diet containing 45% and 60% kcal fat) and NASH (methionine- and choline-deficient diet and choline deficiency combined with high fat diet). We also administered doxorubicin in mice lacking p53 specifically in the liver.
Results
We demonstrate that chronic pharmacological stimulation of p53 with a low dose of doxorubicin (administered intraperitoneally and orally) improves liver injury in different models of diet-induced steatosis and NASH through stimulation of fatty acid oxidation and decrease of lipogenesis, inflammation, and ER stress. These effects did not occur when the drug was administered to mice with liver-specific ablation of p53.
Conclusion
Our results show that long-term pharmacological activation of p53 using intraperitoneal injection or oral administration of doxorubicin at much lower doses than those used in oncology ameliorates liver injury. The attenuation of liver injury was correlated with increased fatty acid oxidation, decreased *de novo* fatty acid synthesis, reduced inflammation, and lowered ER stress. We provide mechanistic insight evidence that these doxorubicin-mediated effects were dependent of p53, since they were not observed in mice where hepatic p53 expression was missing or reduced. These data provide new evidence for targeting p53 as a strategy to treat liver disease.
Acknowledgement
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GP157

Obesity is associated with a dysregulation in the splicing machinery components at the hepatic level: influence of metformin

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Obesity, a multifactorial chronic endocrine-metabolic disease, represents one of the most serious and complex global health threats, as it is commonly associated with multiple and severe comorbidities (e.g. diabetes type-2). Indeed, as a source of severe metabolic-dysregulation, obesity alters physiological, homeostatic gene expression patters in multiple metabolic-tissues, including the central metabolic hub, i.e. the liver. However, the precise molecular mechanisms underlying this pathological association are still unknown. There is emerging evidence that alternative mRNA splicing, the key mechanism providing transcript/protein-diversity from a single gene, is dysregulated in many tissues under adverse metabolic-conditions, such as obesity, and can influence the development and progression of several pathologies. Here, we hypothesized that an alteration in the splicing machinery could occur in key metabolic tissues, such as the liver, during obesity, which might ultimately be associated with the progression of hepatic disease. To ascertain this question, an array of selected components of the major- ($n=13$) and minor-spliceosome ($n=4$), and associated splicing-factors ($n=28$) was developed, and their expression levels were evaluated using a Fluidigm methodology, in the liver of obese mice (fed a high-fat diet) compared with control-lean mice (fed a low-fat diet). Additionally, we analysed whether the splicing processes are regulated by metformin (an agent used to treat type-2-diabetes) in livers of obese vs. control-lean mice. Results revealed that expression of some splicing-machinery factors was altered in the liver of obese vs. control-lean mice (e.g. up-regulation: RNU1, RNU2, RBM22, SRSF3; down-regulation: RNU11). Interestingly, we found that metformin similarly altered the hepatic expression of two splicing-machinery factors (i.e. up-regulation of SRSF10 and PSF) in obese- and lean-mice. However, many other components of the splicing machinery-associated factors (i.e. RNU1, U2AF1, PRPF40A, PRPF8, RBM22, RNU6atac, CELF1, SRSF5, SRSF6, SRSF9, SNW1, SND1, SFPQ, KHDRBS1) were exclusively up-regulated by metformin under normal-lean, but not obese, conditions which might suggest that the liver of obese-mice (which had fatty-liver and were hyperglycemic and hyperinsulinemic) might be partially resistant to alterations in the splicing machinery in response to metformin. Altogether, our results suggest that the alteration of the some components of the cellular splicing machinery in hepatocytes could be responsible for the dysregulated expression of multiple splice variants produced in the liver under obesity conditions. Ongoing studies would clarify the potential physiological implications of these findings, which may provide novel diagnostic biomarkers and therapeutic tools to treat hepatic-diseases.
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GP158

Dietary intake of fat and oil are associated with expression of miR-143 and miR-34a in visceral and subcutaneous adipose tissues of adults: a nutriepigenetic study

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Background and objective
Adipose tissue where energy homeostasis is regulated is now considered an endocrine organ. miRNAs may contribute to the regulation of energy balance and metabolic homeostasis, by controlling a wide range of metabolic pathways. miR-143 and miR-34a are the best studied among the miRNAs linked to adipose tissue regulation. Dietary intake, among many other environmental factors, is a key player that can induce epigenetic changes. The aim of the study was to investigate the association of the miR-143 and miR-34a expression in visceral and subcutaneous adipose tissues with habitual fat and oil intakes.
Materials and methods
Visceral and subcutaneous adipose tissues were obtained from 97 adults (41 non-obese, 18 obese, and 38 morbid obese), who underwent open abdominal surgery with minimal impact on dietary intake. Intake of hydrogenated and non-hydrogenated vegetable oils and butter were collected by using a valid and reliable food frequency questionnaire. The expressions of miR-143 and miR-34a in visceral and subcutaneous adipose tissues were measured by Real-Time PCR. Linear regression models were used to estimate association of dietary hydrogenated and non-hydrogenated vegetable oils and butter intake with miR-143 and miR-34a expression after adjustment for potential confounding variables.
Findings
Expression of miR-34a was more increased in morbid obese than obese subjects in both subcutaneous (13.3 vs 11.3, $P<0.002$) and visceral (13.4 vs 9.2, $P<0.001$) adipocytes. After adjustment for total energy intake, insulin, triglycerides, and age, visceral adipose tissue miR-143 expression was positively associated with total intakes of fats and oils ($\beta=0.334$, $P=0.024$) in the total population. The miR-143expression in visceral adiposity among morbid obese was negatively associated with non-hydrogenated vegetable oils ($\beta=-0.317$, $P=0.036$), and directly associated with butter ($\beta=0.503$, $P=0.002$) intake. The miR-34a expression among morbid obese participants was associated with total fats and oils ($r=0.534$, $P<0.001$) and non-hydrogenated oil ($\beta=0.443$, $P=0.008$) in visceral adipose tissue. Moreover, we found a significant association of miR-143 expression in subcutaneous adipose tissue with butter in both morbidly obese and non-obese participants.

Conclusions
A increase in miR-143 and miR-34a expression by total fats and oils, may explain the development of obesity through high-fat diet. A decrease in expression of miR-143 by non-hydrogenated oils would justify a lower adipogenic capacity and, would, therefore, contribute to the decrease of fat stores observed in adipose tissue with higher intake of fatty acids contains non-hydrogenated oils.

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GP159

Role of Elovl6 in the thermogenic action of brown and beige adipocyte during β3-adrenergic receptor activation

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Recent studies suggest that adult humans have active brown or beige adipocytes, the activation of which might be a therapeutic strategy for the treatment of metabolic diseases. Treatment of CL-316243, a β3-adrenergic receptor agonist, activates brown/beige adipocytes and can cause significant reductions in adiposity. Many transcriptional pathways regulating brown/beige adipose tissue have been identified, the role of lipid biosynthetic enzymes in brown/beige adipose tissue has been less investigated. In this study, we investigated the role of Elovl6, the enzyme responsible for converting C16 non-essential fatty acids into C18 species, in the thermogenic action of brown/beige adipose tissue. We have observed upregulation of Elovl6 in brown adipose tissue (BAT) and inguinal white adipose tissue (iWAT) of mice treated with CL-316243 as well as cold-expose. It was reported that Elovl6 KO mice have impaired mitochondrial function and hence impaired thermogenic capacity of BAT when exposed to cold temperature (*Cell Rep.* 13:2039, 2015). When exposed to chronic CL-316243 treatment we observed that Elovl6 KO mice compensate its impaired BAT function by increased development of functional beige fat contributing to its increased energy expenditure. CL-316243 induces the expression of genes involved in creatine metabolism and mitochondrial biogenesis in the iWAT of Elovl6 deficient mice. Pharmacological reduction of creatine levels by the treatment of β-guanidinopropionic acid (β-GPA) to Elovl6 KO mice decreases whole-body energy expenditure after administration of CL-316243. Our data suggest that Elovl6-regulated FA chain length is important for brown/beige adipose tissue function and creatine metabolism has an important compensatory role in adipose tissue energy expenditure and thermogenesis during impaired BAT function.

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GP160

Physiological regulation of brown adipose tissue in obesity by mild-cold exposure, a B3-agonist and exercise training at thermoneutrality

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Background
Therapeutic activation of thermogenic brown adipose tissue (BAT) is a potential strategy to prevent obesity and metabolic disease in humans. However, it is now recognised that rodent studies examining BAT physiology are carried out at sub-thermoneutral temperatures (e.g. ~20°C), and are not translationally relevant to humans as BAT is 'hyperactive'. Therefore, the aim of this study was to determine the effect of common regulators of BAT metabolism when animals were raised at thermoneutrality (28°C).
Methods
Thirty weanling Sprague-Dawley rats were housed at thermoneutrality (28°C) and randomised to either chow (C, $n=6$) or a high-fat diet (HFD, $n=24$) from 3-weeks of age. At 12 weeks, subgroups ($n=6$) of HFD were randomised to either mild-cold exposure (20°C), Mirabegron, a selective β3-agonist (0.75 mk/kg per day) or exercise training (1 h/d, 5 d/week). Metabolic assessment was undertaken in CLAMS during the last 48 h to assess energy intake (EI), expenditure (EE) and physical activity (PA) in addition to the acute response to administration of Mirabegron. Key thermogenic and metabolic genes were analysed in interscapular BAT by qPCR in addition to targeted insulin resistance PCR Arrays (86 key genes, $n=3$).
Results
No interventions reduced body weight or fat mass. There was no difference in 24 h EE, EI or PA between groups. Key thermogenic genes in BAT were unchanged by the interventions. CITED1 expression was upregulated by HFD and reduced by all interventions whilst PRDM16 expression was reduced by HFD and increased by exercise. Similarly, expression of PPARA, mTOR and the 'beige' marker TBX1 were upregulated by exercise only. Targeted PCR arrays demonstrated an upregulation of inflammatory markers e.g. TLR4, EMR1, CASP1 and IL18R1 and a downregulation of metabolic genes e.g. SCD1, FASN, ACACB, HK2 with HFD. Only FASN, SCD1 and ACACA were upregulated in Cold whilst IL18R1, TLR4 and EMR1 were downregulated. Similarly, β3 increased FASN whilst downregulating IL18R1, IL6 and STAT3. Finally, Exercise upregulated FASN, SCD1, HK, ACACA, ACACB and PDK2 whilst downregulating NLRP3, IL1β and PYCARD.
Conclusion
Whilst there is an intervention specific effect on immune genes in BAT we show there is no consistent upregulation of thermogenic genes in response to common stimuli when animals are raised at thermoneutrality. Effects of interventions to activate BAT carried out at sub-thermoneutrality are most likely to be a consequence of chronic mild-cold stress and are unlikely to be translated to humans.

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GP161

Cold induced thermogenesis is influenced by seasonal changes in outdoor temperature

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Background
Humans and other mammals need to maintain a stable core body temperature. Energy expenditure increases in response to a mild cold stimulus, this is called cold induced thermogenesis (CIT). Recently, thermogenic brown adipose tissue (BAT) has been found to play an important role for CIT in human adults. It is known that energy expenditure and CIT are acutely influenced by ambient temperature. In the present study, we investigated the effect of seasonal temperature variation on CIT in human adults.
Methods
We collected data from two prospective observational studies and the screening data from an interventional trial. The analysed 89 participants all underwent measurement of CIT. Of these, 56 participants were healthy volunteers and 33 were hypothyroid patients at the time of the measurement sufficiently substituted with thyroxin. CIT was measured by indirect calorimetry during warm conditions and after a mild cold stimulus of 90 min. CIT was determined as the difference between energy expenditure (EE) during warm (EE_{warm}) and cold (EE_{cold}) conditions. Skin temperature was measured in the supraclavicular region (TempSC) adjacent to the major human BAT depot and compared with parasternal temperatures (TempPS); the difference between TempSC and TempPS was calculated as an indicator of BAT activity. We analysed the relation ofEE, CIT and skin temperatures to the outdoor temperatures, which were recorded by the Institute for Meteorology, Climatology and Remote Sensing at the University of Basel. Daily temperatures were averaged over a period of 7 (TempMax7d) or 30 days (TempMax30d) prior to the corresponding study visit.
Results
CIT was inversely associated with the average maximum outdoor temperature during the week ($R^2=0.1737$, $P<0.0001$) and the month ($R^2=0.1424$, $P=0.0003$) before the visit date. EE_{warm} and EE_{cold} were not significantly related to outdoor temperatures, EE_{warm}; $R^2=0.0074$, $P=0.4218$ (TempMax7d), $R^2=0.0168$, $P=0.2252$ (TempMax30d) and EE_{cold}; $R^2=0.0132$, $P=0.2840$ (TempMax7d), $R^2=0.0035$, $P=0.5831$ (TempMax30d). The difference between

TempSC and TempPS was also inversely related to TempMax7d, $R^2=0.07575$, $P=0.0221$, indicating increased activation of BAT in response to longer periods of cold temperatures.
Conclusion
CIT is strongly and inversely correlated to outdoor temperatures indicating dynamic adaption of thermogenesis and BAT activity to environmental stimuli in adult humans.

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Paediatrics, Developmental & Female Reproduction

GP162

Biomonitoring infantile urinary sexual hormone profiles for investigation of the endocrine disruptors associated mini-puberty effects

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Many surveys have shown that children are ubiquitously exposed to endocrine disruptors (EDs) like bisphenol A (BPA) and phthalates, and many laboratory studies have shown these EDs have adverse effects related to hormone secretion, while the evidence on infants' mini-puberty has not been observed yet. A prospective cohort was recruited at the early maternal pregnancy stage by the Maternal and Child Health and Family Planning Service Center, Daishan, China, from March 2012 to December 2014. After delivery, the mothers offered their baby (0–6 months old) urine samples collected by the disposable diapers. Urinary BPA, phthalate metabolites, estradiol (E_2), testosterone (T), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and creatinine were analyzed, respectively. The partial correlation and multivariable linear regression were applied to assess the associations of endocrine disruptors with E_2, T, FSH and LH for each of the development stages, i.e., the newborn, 14-days, 28-days, 42-days, 3-months and 6-months, respectively. Firstly, urinary hormones showed the clear surge profiles for the selected hormones during mini-puberty; in addition, the endogenous creatinine releasing was increased with the growth of baby. After adjusted by creatinine, maternal age, end-of-pregnancy weight, parity, smoking, delivery mode and infant body mass index (BMI), BPA was positively associated with E_2 both in male (for 14-, 28- and 42-days stages) and female (for 14-, 28-, 42-days and 3-months stages) infants, positively associated with E_2/T ratio both in male (for 14- and 28-days stages) and female (for 14-days stage) infants, positively associated with T in female (for 3-months stage). To phthalates, their metabolism also changed, in which the di-ester phthalates' hydrolysis may be decreased but the 2nd β-oxidation of the middle and long side chains of the mono-ester phthalates was increased. After adjusted by maternal age, end-of-pregnancy weight, parity, smoking, delivery mode, gender and BMI of infants, some interesting associations were also observed between the phthalate exposure and mini-puberty hormone surges. By using a time-series sampling strategy, this study investigated the early infantile life-stage associated endocrine disrupting of phthalates and BPA to some selected hormones by using urine from diapers. The results showed that the phthalate metabolism in infantile body is changed along with the growth. In addition, the infants' first show of steroids' surge after leaving the maternal uterus steroidogenic environment (i.e., mini-puberty) may be affected by EDs, which disrupt the premature gonad function at some special development windows.

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GP163

Global DNA methylation since early infancy to adulthood in the offspring of women with polycystic ovary syndrome (PCOS)

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DNA methylation is an epigenetic mechanism of gene regulation that can be modified during intrauterine and postnatal life. Pregnant women with polycystic ovary syndrome (PCOS) present elevated androgen and insulin levels, which can affect the DNA methylation pattern of their offspring. Then, we studied the global DNA methylation pattern (GDNAm) in daughters and sons born to PCOS women compared to controls. Daughters (99 born to PCOS and 87 born to control women) and sons (74 born to PCOS and 93 born to control women) were studied at early infancy (2–3 months), puberty (7–17 years) and adulthood (18–35 years). In all of them, a clinical-anthropometric examination was performed and a blood sample was obtained for DNA isolation from peripheral leukocytes. The absolute percentage (%) of GDNAm was quantified using a colorimetric kit (Epigentek). PCOS and control sons showed a different methylation pattern from early infancy to adulthood. Interestingly, sons born to PCOS mothers presented lower GDNAm compared to controls in early infancy (3.0% vs 7.4%, $P=0.043$) and at the beginning of sexual maturation (2.9% vs 7.1%, $P=0.010$). In daughters, there were no differences in the GDNAm pattern from early infancy to adulthood between both groups. Our data indicate that sons seem to be more susceptible than daughters to changes of the GDNAm, mainly in periods of activation of the gonadal axis, such as early infancy and the beginning of puberty.

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GP164

Utilisation of dental services and dental pathologies identified in children and adolescents with osteogenesis imperfecta in the south west of England

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Background
50% of patients with osteogenesis imperfecta (OI) will have dental involvement of some degree including dentinogenesis imperfecta and a severe malocclusion. OI is the most common inherited disorder of bone fragility in children, increasing fracture risk 100-fold.
Aim
To assess the utilisation of tertiary dental services by children and young people with OI attending a supra-regional multidisciplinary OI service and review of the pathology identified and interventions undertaken.
Design
Case notes review of the current caseload of children and young people (0–18 years) with OI at an OI specialist centre. Primary outcome was if an initial dental assessment was arranged in a tertiary dental centre and the corresponding attendance.
Results
Only 49% received a dental assessment. 82% attended the appointment, 18% failed to attend multiple appointments. Those travelling >100 miles had a DNA rate of 47%. Greater the OI severity, the higher the incidence of DI; 7% incidence in Type I OI and 50% in Type III. 48% received bisphosphonate therapy. 33% required GA for extraction of carious teeth.
Conclusion
Due to the prevalence of DI, severe malocclusion and the increased incidence of dental caries necessitating extraction under GA, coupled with the increased use of bisphosphonates, all patients with OI should receive a formal dental assessment in tertiary care.

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GP165

Early childhood BMI rise, the adiposity rebound, associates with PCOS diagnosis and obesity at ages 31 and 46 years – analysis of 46-year growth data from birth to adulthood in PCOS

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Background
The age at adiposity rebound (AR), at which BMI begins to rise after infancy around the age of 5 years, is associated with obesity and metabolic alteration in later life. Given that polycystic ovary syndrome (PCOS) has strong metabolic components, early growth patterns could reveal predisposition for PCOS. Thus, we aimed to investigate the associations of growth trajectories from birth to puberty with PCOS diagnosis,vbody composition and hyperandrogenism later in adulthood.
Materials and methods
In this prospective, population-based longitudinal Northern Finland Birth Cohort 1966 study, women reporting isolated PCOS symptoms at age 31 ($n=651$), or PCOS diagnosis by age 46 ($n=280$) were compared with asymptomatic women ($n=1573$). Growth data from birth to 13 years, weight, height, serum testosterone levels at menarche, 14, 31 and/or 46 years were analyzed. Findings: Women with PCOS had lower birth weight (3406 vs. 3507 g, $P<0.001$), earlier AR (5.19 vs 5.60 years, $P<0.001$) and higher BMI at menarche compared with controls. Early timing of AR associated with PCOS-diagnosis independently from BMI (OR:1.62, Cl: 1.37–1.92). Women with PCOS with early AR had an adverse body composition at age 31 and 46 compared with controls with early AR or PCOS with normal/late AR. Early AR was not associated with serum testosterone levels either at 31 years or 46 years.
Conclusions
Early AR is a risk factor for PCOS and high BMI later in life, thus, children with early AR should be considered at risk for adulthood obesity but also for PCOS. Thus, adolescents with early AR and persisting high BMI at menarche should be screened for PCOS symptoms, such as persisting irregular cycles and hirsutism.

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GP166

Endemic goiter and breasts diseases in adolescent girls

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Research indicates the relationship between beast and thyroid gland. Breast tissue contains the highest concentrations of iodine, so shortfalls in this essential mineral needs have a highly negative impact on breast tissue (R. Thompson, 2015).
Purpose
The study was undertaken to estimate the frequency of the breasts diseases in adolescent girls with endemic goiter.
Patients and methods
The study included 2371 girls (aged 10–18 years). Endemic goiter was diagnosed on the basis of the typical picture of examination and thyroid ultrasound, hormonal analysis. Breast diseases were diagnosed on the basis of clinical signs and typical picture of breast ultrasound. From the girls without thyroid pathology a control group were formed ($n=30$). Statistical analysis was performed using Mann-Whitney Test. This study has been carried out in accordance with the Helsinki Declaration.
Results
The endemic goiter was diagnosed in 685 (29%) girls. Thyroid function was normal in all girls; however, in comparison group the average TSH levels were 2.8 ± 0.7 and in control group – 1.7 ± 0.5 mIU/l ($P=0.033$). The investigation shows that in adolescent girls with endemic goiter were diagnosed breast cysts (in 29% cases); fibroadenoma was revealed in 2 patients. All second girls with endemic goiter had cyclic (premenstrual) mastalgia, only 2 girls without thyroid pathology had predmenstrual mastalgia and 1 girls had breast cysts (<0.001). All girls with breast dysplasia and fibroadenoma complained of mastalgia too.
Conclusions
This study has shown a high frequency of the breast diseases among the adolescent girls with endemic goiter. Endemic goiter is risk factor for breast diseases and shows the necessity of for observation and examination of breast.

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GP167

Impact of fetal exposure to testosterone on fetal insulin sensitivity tissues in female sheep: a morphological and molecular approach

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PCOS is one of the most common cause of infertility in women during their reproductive years. High proportion of women with PCOS develop IR in peripheral tissues like skeletal muscle and adipose tissue, which may begin at the adolescent years when young women exhibit an increase in circulanting androgens. Studies in women with PCOS and animal models of PCOS have suggested alterations in insulin signaling pathways in skeletal muscle and adipose tissue. However, at the present time, it does not exist evidence between alteration on insulin signaling in endocrine pancreas and its correlative effect on peripheral insulin sensitivity tissues. Previous results from our group have demonstrated that female sheep born to mothers receiving T between days 30 to 120 of gestation exhibit features of insulin resistance from early postnatal stage to adulthood. In the present work, the reprogramming effect of prenatal T on adipose tissue morphology and the insulin signaling in adipose tissue was studied in postpubertal females born to untreated mothers (C-females) and born to T treated mothers (T-females), subjected to a further T administration at the pubertal age. Our aim was to identify if a further T treatment during pubertal development could affect pancreas and adipose tissue. Postpubertal C-females and T-females (38 weeks of age) were sacrificed after an eight week chronic T administration and samples of pancreas, SAT (subcutaneous adipose tissue) and VAT (visceral adipose tissue) were collected. The morphological analysis of the adipose tissue included measurements of area, perimeter, diameter and adipocyte number/mm^2. Results showed no difference ($P\geq0,05$) in morphological parameters between C- and T-females in SAT. However in VAT, the adipocyte area, perimeter, diameter was higher in T-females than in C-females. Gene expression of IR, IRS-1, PI3K, PKC in pancreas showed similar expression in T-females ($P\geq0.05$) compared to that of C-females, while, on the contrary, the Akt and GLUT4 RNAm was lower in T-females ($P<0.05$). Interesting, IRS-2 transcript showed a tendency to a higher expression ($P\geq0.05$) in T-females. qPCR assays of SAT showed a transcriptional repression of IRS-1, PKC, Akt and GLUT4 ($P<0.05$) in T-females. In VAT, insulin signaling did not show effect on expression of pathways elements, except higher Akt levels of RNAm in T-females ($P<0.05$). Results suggest that prenatal and postnatal exposure to T affects the insulin signaling on beta cells during post pubertal development and induced a dual effect in adipose tissue at the transcriptional and morphological levels.

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GP168

Self-esteem, emotional stability, social anxiety disorder and suicidal behaviours among transgender youth before gender-affirmative treatment in spain

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Introduction
The demand of health care for people with gender incongruence (IG) has grown exponentially especially in young population. Due to this, there is a growing number of studies that show psychological conflicts and social functioning in those individuals who have not received gender-affirming treatment with medical intervention (pubertal block, hormone or surgical treatment) and social intervention. However, the data published so far do not represent the European countries, they are an adult population and without a control group.
Aims
To assess the prevalence of psychomorbidity among transgender youth before gender-affirmative treatment.
Methods
Prospective observational study comparing young people between 13–21 years of age cared by GI, evaluated before starting hormonal treatment and at puberal stage at least 2–3 Tanner tested by levels of E2, testosterone, FSH and LH. Direct clinical interview and standardized tests were carried out: low self-esteem, social phobia, emotional inestability, suicidal ideation, suicide attempts and self-harm. The results were compared with those obtained in a population subjected to stress due to sexual orientation (cisgenders): 'homosexuals, lesbians and bisexuals' (LGTB) between 15 and 21 years. The follow-up was in the 'Gender Identity Unit of the Doctor Peset University Hospital' between 2014 and 2016. Those in prepubertal stage and/or who did not meet criteria for treatment initiation were excluded from the study.
Results
A total of 82 interviews were evaluated: 41 in each comparable age group. 51% of individuals with IG developed low self-esteem compared to 34% in the LGTB group ($P=0.118$); 83% moderate-high emotional instability and 44% LGTB group ($P<0.001$); 17% in the IG group developed social anxiety and 34% in LGBT individuals ($P=0.077$. The prevalence of suicidal ideation was 46% and 20% ($P<0.001$), with suicide attempt of 20% compared to 5% ($P=0.043$) and/or self-injury in 29% compared to 5% ($P=0.003$) in the group of individuals with IG with respect to the LGTB group, respectively. The risk of presenting psychomorbidities in the GI group regarding the LGTB group was evaluated through an odds ratio with a result of 2.26 times more risk.
Conclusions
– Low self-esteem and emotional instability are the most prevalent psychomorbidity in both groups; the latter is more frequent in the group with IG.
– Serious conflicts: attempts, suicidal ideation and self-harm are more prevalent in the group with IG.
– The group of individuals with GI present 2.26 times more risk of developing psychomorbidity than the LGTB group.

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GP169

Glucose transporters in human placenta and its relation to birth weight

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Background
Birth weight is a marker and predictor of metabolic diseases in adult life. Fetal growth depends on the availability of nutrients, in turn cross the placental barrier by means of special cells called syncytiotrophoblasts, which express specific transporters for each type of nutrient. Glucose, the main energetic substrate for fetal development, is transported via facilitated diffusion, through glucose transporter proteins (GLUTs). Several investigations have focused on the study of GLUT-1 and GLUT-3 transporters in placental samples from women with complications during pregnancy. Therefore, our study objective was to determine the role of glucose transporters in palcental tissue of clinically healthy women, as well as its relationship with alterations in birth weight.
Methods
Placental samples from clinically healthy women were included in the study, SGA ($n=20$), AGA ($n=20$) and SGA ($n=20$). Placental homogenates were prepared for the evaluation of the expression of glucose transporters (GLUT-1 and GLUT-3) in the 3 study groups by Western Blot. Anti-GLUT1 and anti-GLUT-3 antibodies were used to detect GLUT1 and GLUT-3 (1 : 1500 and 1 : 500 respectively) and were incubated by 20 h. As secondary antibodies were used Anti-Rabbit (1 : 125 000) and anti-Mouse (1 : 5000) antibodies to detect anti-GLUT1 and anti-GLUT-3 respectively, with an incubation time of 2 h. Glucose transporters expression was normalized with the expression of the α Tubulin protein.
Results
Expression of GLUT-1 transporter in placentas of LGA group was 50% higher in comparison to SGA group ($P=0.018$). There were no significant differences in expression between LGA groups vs AGA ($P=0.087$) and SGA vs. AGA ($P=0.492$).
Conclusion
In placentas of infants small and large for gestational age (SGA and LGA) who do not have an adequate weight at birth, there is a differential expression of GLUT-1 transporter. This suggests that this transporter may be important in determining birth weight and, consequently, in the risk of diseases of adult life.

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GP170

Association of glucocorticoid receptor gene (*NR3C1*) expression in HUVECs with glycemic targets during gestational diabetes treatment: a pilot randomized controlled study

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Background
Gestational diabetes mellitus (GDM) is known to predispose offspring to metabolic diseases. However, the underlying mechanisms has not been thoroughly studied yet. The glucocorticoid receptor gene or nuclear receptor sub-family 3, group C, member 1 (*NR3C1*) may predispose to type 2 diabetes mellitus, metabolic syndrome and depression. *NR3C1 gene* showed significantly decreased methylation levels in cord blood and placenta from GDM women compared with controls. Our aim was to study the level of expression of *NR3C1 gene* in human umbilical vein endothelial cells (HUVECs) of newborns from women with GDM depending on glycemic targets.
Materials and methods
The study included 52 women with GDM and 25 women without GDM (control group). GDM patients were randomized to 2 groups per target glycemic levels: GDM1 (more tight glycemic targets, fasting blood glucose <5.1 mmol/l and <7.0 mmol/l postprandial, $n=28$) and GDM2 (less tight glycemic targets, <5.3 mmol/l and <7.8 mmol/l, respectively, $n=24$). The diagnosis of GDM was based on IADPSG criteria. HUVECs were isolated, expanded *in vitro* up to passage 2 and tested for viability and replicative senescence. The level of genes expression was determined by RT-PCR. Women with GDM kept electronic nutrition and glycemic control diaries with the help of a specially developed mobile application and sent data to the doctor. According to the personal diaries automatic calculations of integral indicators characterizing self-control of glycaemia (mean fasting and postprandial glycaemia) and food intake (amount of carbohydrates, proteins, fat and kalories) were accomplished. Statistical analysis included Kruskal-Wallace test, Mann-Whitney test and Spearman correlations.
Results
The level of *NR3C1* gene expression was significantly lower in GDM1 and GDM2 group compared to controls (2.3 ± 0.8, 2.4 ± 1.2, and 3.1 ± 1.2, respectively, $P=0.005$), with no difference between GDM1 and GDM2. Age and pregestational BMI did not differ among the three groups. Some negative correlations have been observed between the level of *NR3C1* gene expression and the following parameters: fasting plasma glucose (PG) level ($r=$-0.331, $P=0.004$) and 2 h PG in OGTT ($r=-0.253$, $P=0.033$), fasting blood glucose (BG) ($r=-0.397$, $P=0.003$), and postprandial BG ($r=-0.276$, $P=0.046$) measured by participants during the study.
Conclusion
NR3C1 gene expression was down regulated in HUVECs of newborns from GDM mothers and was associated with fasting and postprandial levels of BG during GDM treatment. However, it was not associated with prespecified glycemic targets.

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GP171

Autoimmunity markers in turner syndrome patients

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Background
Turner syndrome (TS) predisposes to autoimmune diseases such as thyroiditis, coeliac disease, diabetes mellitus type 1, inflammatory bowel diseases, alopecia and vitiligo. The prevalence of autoimmunity increases with age and more than one autoimmune disease can coexist together in one patient. The possible factors leading increased autoimmunity in TS are not clear.
Aim
To compare the panel of autoimmunity markers in 37 TS girls (40.5% with 45,X) with the control group of 11 short healthy girls.
Method
Morning blood tests were performed to analyze total lymphocytes, CD3, CD4, CD8 CD4/CD8. CD19, NK, Treg, IgA, IgM, IgG, TGFβ, IL10, anti-TPO, anti-TG and anti-GAD.
Results
The mean ± s.d. age and BMI values in both, study and control, groups were comparable (11.9 ± 4.1 vs 12.5 ± 4.0 years; 19.2 ± 3.3 vs 19.7 ± 4.6 kg/m^2, $P > 0.05$). TS girls presented lower IgG concentration, CD4% and lower CD4/CD8 ratio comparing to healthy controls (9.1 vs 11.5, $P = 0.02$; 32.6% vs 40.4%, $P = 0.0004$; 1.2 vs 1.8, $P = 0.0005$). Further analysis showed that CD4% was the lowest ($P = 0.001$) in girls with isoXq who showed also the highest incidence of elevated thyroid antibodies. Although without statistical significance but girls with three copies of genes from Xq presented also the lowest Treg and the highest CD8. The remaining laboratory markers were comparable between study and control group and did not show any difference when girls with 45,X, 45,X/46,XX and other TS karyotypes were analyzed separately.
Conclusions
We confirm in TS the lower ratio of CD4/CD8 but in contrast to previous studies, besides girls with isoXq, it was not the result of higher number of CD8. IsoXq was found a risk factor for higher incidence of autoimmunity in TS.

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Parathyroid

GP172

A pilot study of the differences in miRNA expression profile in the blood serum between patients with malignant and benign parathyroid tumors

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Background
MiRNAs are small non-coding RNAs, which regulate biological and pathological processes, including organogenesis, apoptosis, cell proliferation and differentiation. Considering the complexity of the parathyroid cancer (PC) diagnosis, discovering of new markers of the disease, which may help to evaluate the prognosis before surgical treatment, becomes an important problem. We studied the differences in miRNA expression profile in the blood serum between patients with malignant and benign parathyroid tumors for better understanding of the molecular processes, which may play a role in parathyroid tumorigenesis and may serve as diagnostic markers for PC.
Aims
To develop a specific miRNA panel for the differential diagnosis of the carcinoma of the parathyroid glands (PG).
Materials and methods
Serum samples were taken from persons with clinically and laboratory confirmed primary hyperparathyroidism (PHPT) and stored frozen at −20°C. After the morphological analysis of postoperative material, the patients were divided into 2 groups: patients with adenomas of the PG ($n = 6$) and patients with cancer of the PG with metastasis ($n = 6$). To perform a simultaneous comparative expression analysis of 760 microRNAs, the «TaqMan OpenArray Human MicroRNA Panel» (Thermo Fiher) was used in conducting of real-time PCR reaction on «QuantStudio 12K Flex» station.
Results
We detected 14 miRNAs which level was significantly lower in patients with parathyroid carcinoma in compare to miRNAs in patients with parathyroid adenoma: miRNA-186 ($P = 0.006$), miRNA let-7e ($P = 0.019$), miRNA-195 ($P = 0.009$), miRNA 16 ($P = 0.005$), miRNA-15b ($P = 0.037$), miRNA-146b ($P = 0.037$), miRNA-19b ($P = 0.004$), miRNA-106b ($P = 0.018$), miRNA-126 ($P = 0.043$), miRNA 342-3p ($P = 0.005$), miRNA-17 ($P = 0.017$), miRNA-320 ($P = 0.039$), miRNA-25 ($P = 0.005$), miRNA-93 ($P = 0.037$).
Conclusions
The pilot study showed that 14 miRNAs could help to differentiate benign tumors from malignant tumors before a surgery and predict metastases. The next step of this study would be the analysis of the sensitivity and specifity of the result on a bigger sample of patients.

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Excess of parathyroid hyperplasia incidence in subjects exposed to ionizing radiation after the CHNPP accident

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Parathyroid glands are critical not only for regulation of the phosphorous-calcium metabolism, but also have a key role in the function of nervous, cardiovascular, digestive and other human body systems. Parathyroids are capable of accumulating the isotopes of cesium, strontium and radioactive iodine, which can lead to parathyroid cell damage and emergence of glandular dysfunction. Significant radioactive environmental releases and fallout after the Chernobyl NPP accident in 1986 were followed by incorporation of the, first and foremost, isotopes of iodine, cesium and strontium, which on top of that were accumulated in parathyroids. Since radioactive iodine is both alpha- and beta-emitter the accumulation of it in large amounts by the thyroid results in the secondary irradiation of parathyroids. Just similar situation is characteristic for the Fukushima NPP accident. Radiation exposure of parathyroids leads to the onset of related disorders of other systems. Unfortunately, we have started such a long-term research for the first time only now, i.e. about 30 years after the exposure of the survived people. We have now the very first important results here. Namely the 686 adults and 54 of their first-generation descendants were examined, and the obtained data testify to an increase in the incidence (28.64%) of clinically important parathyroid hyperplasia (more than 9 mm in adults, and more than 5 mm in children) among subjects irradiated after the Chornobyl accident, especially in the clean-up workers for a long time involved in recovery operations in the Chornobyl zone, and in their descendants (23.8–70.6%). Those adult subjects who live in areas contaminated by radioactive strontium and cesium are of especial concern when compared with the control group of unexposed subjects (24.15% incidence). The evacuees from the 30-km Chornobyl exclusion zone are the another group of risk as they were exposed from the incorporated iodine isotopes in the early days of the Chornobyl accident. Some detected abnormalities were not linked to the functional state parathyroids or lack of vitamin D. Continuation of the research will clarify the causative relationships here.

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The design and preliminary results of a phase 1 TransCon PTH trial in healthy volunteers

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Background
Hypoparathyroidism (HP), a condition of parathyroid hormone (PTH) deficiency, leads to abnormal calcium metabolism. Standard of care (SOC), ie, large amounts of calcium and active vitamin D, leads to hypercalciuria and increased calcium x phosphate. Daily Natpara, PTH(1-84), injections reduced calcium and active

vitamin D doses but not 24-hour urinary calcium (uCa) excretion or incidence of hypo- and hypercalcemia due to its 3-hour half-life (Natpara label). NIH studies of PTH(1-34) in children and adults with HP have shown that a single subcutaneous (SC) injection is superior to SOC, twice daily injections are superior to once daily, and continuous SC infusion normalizes serum calcium (sCa), serum phosphate (sP), and uCa. Ascendis Pharma is developing TransCon PTH, an inactive prodrug of PTH(1-34) for the treatment of HP. In its prodrug form, PTH(1-34) is transiently bound to the TransCon carrier via the TransCon linker. Through autohydrolysis at physiological temperature and pH, unmodified PTH(1-34) is released, providing free PTH at steady state with an infusion-like profile in the physiological range over 24 h.

Methods

This phase 1, randomized, placebo-controlled, single and multiple ascending dose (SAD and MAD) trial evaluated safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of TransCon PTH in up to 170 healthy adults. Cohorts consisted of 10 subjects (8 active, 2 placebo) and received 7 SAD (3.5, 12, 32, 48, 72, 100, or 124 μg) or up to 9 MAD (3.5, 7.0, 12, 16, 20, 24, 32, 40, and 48 μg) for 10 days. The primary PD endpoints included sCa, uCa, sP, and PTH(1-84). The primary PK endpoint was free PTH.

Results

The completed SAD and MAD cohorts showed TransCon PTH was well-tolerated without DLTs. The PK showed dose-dependent increases in exposure, with $T_{1/2}$ of approximately 60 h. Single injections up to 100 μg showed dose-dependent increases in albumin-adjusted sCa (up to 11.0 mg/dl at 100 μg) sustained for $\geq$72 h and associated with reductions in PTH(1-84) but without change in fractional excretion of Ca (FECa). The trial is ongoing; 7 SAD cohorts and several MAD cohorts, including relevant phase 3 doses, will be presented.

Conclusion

TransCon PTH is being developed for HP as a once-daily SC injection. Interim data supports a normal range infusion-like PTH profile, with a PTH $T_{1/2}$ of approximately 60 h and sustained increases in sCa without change in FECa, potentially addressing limitations of available HP therapies.

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GP175

Diagnosis and management of pseudohypoparathyroidism and related disorders: first international consensus statement

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Pseudohypoparathyroidism (PHP) and related disorders lead to a wide spectrum of abnormal physical characteristics, neurocognitive and endocrine abnormalities that share a common PTH/PTHrP signaling pathway. The clinical and molecular overlap of PHP and related disorders lead to difficulties in clinical and molecular diagnosis which prompt to the possibility of incorrect management of these patients. PHP (including all subtypes), pseudoPHP, acrodysostosis and progressive osseous heteroplasia refer to heterogeneous disorders characterized by physical findings, differently associated in each subtype, including short bones, short stature, a stocky build, subcutaneous ectopic ossifications (features associated to Albright Hereditary Osteodystrophy, AHO), as well as laboratory abnormalities such as hypocalcemia, hyperphosphatemia, and elevated PTH and TSH levels. Other features have been attributed to these disorders, such as intra uterine growth failure, early-onset obesity, hypogonadism, hypothyroidism, elevated calcitonin levels, growth hormone deficiency and neurocognitive deficiency. The main subtypes of PHP and related disorders are caused by *de novo* or autosomal dominantly inherited inactivating genetic mutations, and/or epigenetic, sporadic or genetic-based alterations within or upstream of GNAS, PRKAR1A, and *PDE4D* and PDE3A. Over the past 30 years, incredible progress has been made on the pathophysiology of these disorders throughout the world by physicians and research networks. However, caregivers and patients are lacking guidelines for the daily life management of patients. Our aim was to help them from the clinical diagnosis, to the molecular confirmation of the genetic or the epigenetic defect, up to the management of the most frequent manifestations of these rare diseases. Therefore, a consensus statement was prepared for 2 years to produce recommendations for clinical and molecular diagnosis and management of patients with PHP and related disorders. The approach comprised 2 pre-consensus meetings, an expert consensus meeting, and a Delphi-like methodology, adjusted to rare diseases. This consensus meeting was supported by several patients' associations and scientific societies, including the ESE. After a comprehensive literature search using PubMed, >800 papers published since 1 January 1990 to 18 December 2016 have been reviewed and recommendations on

clinical and diagnosis and management on PHP and related disorders have been voted and approved with different levels of evidence: 14 recommendations on clinical diagnosis, 11 on molecular diagnosis and 39 on management and treatment.

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Symptom burden and HRQoL reported among patients with chronic hypoparathyroidism: impact of treatment with rhPTH (1-84) and with standard therapy

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Chronic hypoparathyroidism (HypoPT) is a rare disease associated with a variety of symptoms and diminished health-related quality of life (HRQoL). This study aimed to characterise and quantify the symptom burden, HRQoL, and overall disease impact in patients receiving recombinant human parathyroid hormone (rhPTH1-84, Natpar®) for inadequately controlled HypoPT and in symptomatic patients receiving standard therapy (ST; calcium and/or vitamin D supplements). A web-based patient survey was developed with input from members of the US Hypoparathyroidism Association and from physician experts. Eligibility criteria included receiving rhPTH1-84 or having symptoms of HypoPT while on ST. All respondents were $\geq$18 years old, US residents, diagnosed with HypoPT, and currently taking prescription and/or over-the-counter therapies to manage their condition. The surveys were completed at one point in time and focused on patient characteristics, recall of symptom burden from prior to and while taking their current treatment, impact of HypoPT on life and work, and HRQoL evaluated by SF-36 v2. 90 patients (mean age, 54 years; women, 83%) with HypoPT (mean duration, 8.8 years) currently on rhPTH1-84 (mean duration of therapy, 19 months) and 47 patients (mean age, 50 years; women, 93%) with HypoPT (mean duration, 16.3 years) currently symptomatic on ST completed the survey. Patients on rhPTH1-84 experienced an average of 9.1 symptoms (range, 0–34) and patients on ST experienced an average of 20.2 symptoms (range, 1-39) over a recall period of up to 12 months. Patients currently on rhPTH1-84 recalled experiencing an average of 17.0 symptoms (range, 3–40) prior to rhPTH1-84 therapy. A numerically greater proportion of patients on ST reported significant disease-associated interference with their lives (49%) and impact on work responsibilities (31%) versus patients on rhPTH1-84 (27% and 15%, respectively). rhPTH1-84 patients scored numerically higher on HRQoL (SF-36v2 domain scores range, 44.8-49.8) compared with ST patients (range, 33.9–40.9). HypoPT is associated with significant symptom burden. Patients on rhPTH1-84 recalled a reduction in symptoms after starting therapy, while most patients on ST reported minimal improvement of their HypoPT-related symptoms. Patients on rhPTH1-84 reported numerically higher physical and mental domain scores as measured by SF-36v2 (higher score indicating better HRQoL) compared with ST patients. This cross-sectional real-world non-interventional study does not control for unobserved treatment selection bias and underlying clinical differences that may impact treatment effectiveness between treatment groups. Retrospective reporting of baseline symptoms and other questions, which depend on patient recall represents an additional limitation.

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Maintenance of key biochemical parameters with recombinant human parathyroid hormone (1-84) in patients with hypoparathyroidism: an analysis of a long-term, open-label, single-centre study

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Hypoparathyroidism is a rare disorder characterised by hypocalcaemia and insufficient or undetectable parathyroid hormone (PTH). Recombinant human PTH, rhPTH(1-84), has been approved in the United States and Europe as an adjunctive treatment for adult patients with hypoparathyroidism. When hypoparathyroidism is established, long-term administration of rhPTH(1-84) is a treatment option. Thus, long-term safety and efficacy data for rhPTH(1-84) are needed. To this end, we evaluated data from adults with hypoparathyroidism who previously participated in a single-arm, single-centre study known as HEXT (NCT00473265) and are now enrolled in a new phase 4 study (NCT02910466). Uninterrupted rhPTH(1-84) therapy has been maintained for 4.0 to 11.4 years. Baseline was the last assessment before starting rhPTH(1-84). Visit windows, defined as once every 6 ± 3 months from baseline, were used for summary of assessments collected over time from medical records. If multiple measurements were recorded within a visit window, the value closest to the target day was used. Data are presented as mean $\pm$ SD.. This cohort comprises 33 patients (53.4 ± 12.4 years; 76% women; duration of hypoparathyroidism, 19.4 ± 12.1 years). Mean duration of rhPTH(1-84) treatment was 7.5 ± 2.3 years. Albumin-corrected serum calcium remained relatively stable during the treatment period and was near or within the target range for patients with hypoparathyroidism at most time points. Urinary calcium, serum phosphate, and serum creatinine were maintained within the target or normal ranges at all time points during rhPTH(1-84) treatment. Estimated glomerular filtration rate was between 60 and 89 ml/min per 1.73 m^2 at baseline and at most time points over the course of rhPTH(1-84) treatment. Calcium-phosphate product was 3.06 ± 0.55 $mmol^2/l^2$ at baseline and remained <4.4 $mmol^2/l^2$ at all time points. This analysis includes the longest reported experience with rhPTH(1-84) for the treatment of hypoparathyroidism. The results document that rhPTH(1-84) treatment is characterised by maintenance of biochemical parameters, including stable renal function, within normal or target ranges for this disease. These data provide strong support for the efficacy of rhPTH(1-84) in the long-term management of hypoparathyroidism.

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The global, prospective, observational PARADIGHM™ registry for patients with chronic hypoparathyroidism was expanded to capture recombinant human parathyroid hormone, rhPTH(1-84), use under routine clinical care

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PARADIGHM™, a global, prospective, observational registry of patients with chronic hypoparathyroidism (HPT), began enrolment in 2013 to collect data on the natural history of chronic HPT (ClinicalTrials.gov NCT01922440). Since initiation, recombinant human PTH, rhPTH(1-84), has been approved in the United States and Europe as an adjunctive treatment for adult patients with HPT. The protocol for the registry (now a European Medicines Agency–designated postmarketing commitment) was amended to capture rhPTH(1-84) use in HPT patients under routine clinical care (EUPAS16927). Patient recruitment continues with a global enrolment goal of $\geq$900 patients, including $\geq$300 receiving rhPTH(1-84). Follow-up data collection on each patient is planned for $\geq$10 years. Patients with a diagnosis of HPT of $\geq$6 months are eligible for inclusion; exclusions include inability to provide informed consent, enrolment in any interventional study, or active PTH(1-34) therapy. Treatment regimens are determined by the patients' physician, per usual clinical practice, and can be conventional calcium/vitamin D supplements and/or rhPTH(1-84). Primary outcome variables are HPT lab tests, including renal function; renal and cardiovascular events; soft tissue calcification or bone fractures; presence of cataracts; and adverse events, including those considered to be related to rhPTH(1-84) treatment. Secondary outcome variables include health-related quality of life, disease-specific patient-reported measures, and hospitalisations

and emergency room visits. Additional data to be collected include demographics, medical history, HPT management, and concomitant medications. Data are collected every 6 months, and the database uploads are via electronic data capture. A steering committee reviews scientific reports and evaluates requests for analyses. Prior to starting the new protocol, a registry data cut on December 1, 2016, was completed. Forty-one investigator sites and 492 patients (49 ± 17 years of age; 30 ± 9 kg/m^2 body mass index) had been enrolled. Notably, 93% of patients reported ≥ 1 symptom within the previous 6 months despite prescribed conventional therapy of calcium (91%) and vitamin D (84%). Only 7% were recorded as receiving rhPTH(1-84) in a clinical trial setting (ie, data capture was prior to US Food and Drug Administration approval). Data from PARADIGHM will provide physicians with needed information on the natural history of HPT in patients prescribed conventional treatment and in those prescribed rhPTH(1-84).

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Stone risk profile analysis in patients with asymptomatic primary hyperparathyroidism

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The kidney is an important target of primary hyperparathyroidism (PHPT). The 4th International Workshop for the management of Asymptomatic PHPT included the presence of hypercalciuria (24-h urinary calcium > 400 mg/day) and increased stone risk by biochemical stone risk profile as criteria for surgery. Increased stone risk profile was defined as at least one between ßCaOx > 4 and ßHPO4 > 2, as defined in literature in a different study population. The aim of the present study was to evaluate the stone risk profile in 102 consecutive patients with asymptomatic PHPT, enrolled from October 2016-June 2017. We recorded clinical and biochemical data, kidney ultrasound and urinary stone risk profile by LithoRisk software, that calculates urine state of saturation for calcium oxalate (ßCaOx) and calcium hydrogen phosphate or brushite (ßHPO4). The group included 81 females and 21 males, mean age 55 ± 15 years. In 93 (91%) patients were sporadic and in 9 (9%) had MEN1 syndrome. We found clearance of creatine < 60 ml/min in 4.9% (n = 5) and nephrolithiasis/nephrocalcinosis ultrasound detected in 18.3% (n = 19). Hypercalciuria (24 h urinary calcium > 400 mg/24 h) was detected in 29.4% (n = 30). It was present in 57.9% (11 out of 19) patients with kidney stones detected at ultrasound (stone carriers) and in 22.9% (19 out of 83) of those patients without ultrasound detected stones. Either in the former and in the latter group all patients with hypercalciuria had also an increased stone risk profile. Moreover, we evaluated the stone risk profile also in those patients "stone carriers" without hypercalciuria (n = 8) and we found that in 5 patients it was increased. In the whole group we found a positive correlation between ßCaOx and PTH (P = 0.029, r = 0.25) and between ßHPO4 and PTH (P = 0.015, r = 0.27). Our data suggest that hypercalciuria alone can identify all patients with positive stone risk profile. However, in the group of patients with stones detected at ultrasound and 24-h- urinary calcium < 400 mg/24 h there is a proportion of patients in which Lithotest® can detect an increased stone forming risk.

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GP180

Five-year efficacy and safety of recombinant human parathyroid hormone 1-84 (rhPTH[1-84]) for the treatment of adults with chronic hypoparathyroidism: analysis from the open-label RACE study

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Hypoparathyroidism is a disorder of mineral homoeostasis due to parathyroid hormone (PTH) deficiency. Conventional treatment with oral Ca and calcitriol may maintain serum Ca levels but does not replace other physiologic PTH effects. RACE is an ongoing open-label study of recombinant human PTH1-84 (rhPTH1-84) for hypoparathyroidism treatment in adults (ClinicalTrials.gov NCT01297309). Patients initially received rhPTH1-84 25 or 50 µg/day subcutaneously, with 25-µg increases to 100 µg/day maximum. rhPTH(1-84) could be titrated and oral Ca/calcitriol doses adjusted at any time during the study to maintain serum Ca levels within the optimised target (2.0–2.2 mmol/l). Primary objective was to demonstrate the long-term safety and tolerability of rhPTH1-84. Composite efficacy endpoint was the proportion of patients who achieved a ≥50% reduction from baseline (BL) in oral Ca dose (or Ca ≤500 mg/day) and a ≥50% reduction from BL in calcitriol dose (or calcitriol ≤0.25 µg/day) while maintaining albumin-adjusted serum Ca between 1.87 mmol/l and the ULN for the central laboratory. Five-year, open-label efficacy and safety data presented with descriptive summary statistics (mean(s.d.)). Study cohort included 49 adult patients enrolled at 12 US centres (age 48.1[9.78] years; 81.6% female); 40 patients (81.6%) completed 60 months (M60) of rhPTH(1-84) as of 8 May 2017. Oral Ca and calcitriol doses were reduced by 53.4% and 75.7%, respectively; albumin-adjusted serum Ca levels were maintained within the target range (M60, 2.1[0.20] mmol/l; BL, 2.1[0.17] mmol/l). At M60, the efficacy composite endpoint was achieved by 28/40 patients. Urinary Ca excretion showed a numerical reduction (M60, 6.2[3.30] mmol/24 h; BL, 8.9[5.01] mmol/24 h, n = 48), as did serum P levels (M60, 1.3[0.21] mmol/l; BL, 1.6[0.19] mmol/l,) and Ca-P product levels (M60, 2.8[0.45] mmol^2/l^2; BL, 3.4[0.51] mmol^2/l^2). Serum creatinine levels remained stable (M60, 81.7[19.85] µmol/l; BL, 84.7 ± 18.16 µmol/l), as did estimated glomerular filtration rate (M60, 108.1[42.32] ml/min; BL, 108.2[36.36] ml/min, n = 41). Treatment-emergent adverse events (TEAEs) were reported in 48/49 patients. Common TEAEs (>25% of patients) reported included symptoms of the underlying disease (ie, hypocalcaemia [36.7%], muscle spasms [32.7%], paraesthesia [30.6%]), sinusitis (30.6%), and nausea (30.6%). Serious TEAEs occurred in 13 patients. Continuous use of rhPTH1-84 over 5 years has an acceptable safety profile, was well tolerated, efficacious, and improved key measurements of mineral homoeostasis.

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GP181

Is there HIV-associated hypoparathyroidism?

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Background
Parathyroid hormone (PTH) secretion in response to hypocalcemia was found to be altered in people living with HIV (PLWH) and HIV infection has therefore been acknowledged as a potential reason for hypoparathyroidism (HPO).
Aim
To describe the prevalence of HPO in a population of PLWH.
Methods
Monocentric, retrospective sub-study of the Munich ArcHIV cohort.
Results
579 patients (461 men (79.6%)) were included in the study with a median age of 48 (40–54) years. In 496 patients, albumin concentration was available in and the prevalence of HPO was 15.3% (n = 76) and 8.3% (n = 41) in 2016 and 2017, respectively. In 14 patients (1.4%) HPO was found in both years. One of these patients presented with a medical history of cervical irradiation due to Hodgkin's lymphoma. Of 14 patients with HPO in both years, 10 (71.4%) were on tenofovir disoproxil fumarate (TDF) at the time of PTH measurement in both years (P = 0.008). Therefore, exposure to TDF was associated with a risk ratio of 4.2 (1.3–13.1).

Discussion
The prevalence of HPO in our cohort of PLWH was unexpectedly high at 1.4%. Except for one patient, no "traditional" explanation for hypoparathyroidism could be found. Different from findings in "classical" hypoparathyroidism, phosphate levels were not higher in patients with HPO compared to controls; contrary, we even found a trend towards a higher frequency of at least one episode of hypophosphatemia. This might however be attributable to the more frequent use of TDF in patients with HPO, as TDF has been associated with increased phosphate excretion and lower phosphate levels before.
Conclusion
HIV-infection and antiretroviral therapy seem to be associated with a higher prevalence of HPO. The limitations of a retrospective study warrant further investigations on this topic.

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GP182

Use of a Disease-Characteristic Questionnaire identified pain and cramps and neuro-vegetative symptoms as significantly elevated and affected by Medication in mainly well-controlled hypoparathyroid patients

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Introduction
Hypoparathyroidism (hypoPT) is characterized by inadequately low circulating concentrations of parathyroid hormone (PTH) followed by low calcium and increased phosphate levels in the blood. Patients with hypoPT suffer from a number of complications and complaints including infections, neuro-psychiatric diseases, abnormal bone architecture impaired muscle function and reduced quality of life. Due to the complexity of the various clinical manifestations there is a demand for a disease-sensitive control instrument to be able to monitor symptoms beside biochemical values. We used a new disease-characteristic questionnaire to investigate hypoPT patients' complaints and contributing factors.
Methods
This prospective study was conducted in two endocrinological centers in Germany over one year. Patients with postsurgical hypoPT ($n=49$) were matched for sex and age ± 3 years and compared to patients with thyroid surgery without hypoPT (ThySu, $n=39$)) and patients with (former) primary hyperparathyroidism (pHPT, $n=35$). The Hypoparathyroid Patient Questionnaire (HPQ 40) was filled in during the patient's visit at the center. Information was completed by clinical background information (e.g. disease complications), blood tests and current medication. The influence of these clinical data on patients' complaints represented as subscales of the HPQ 40 (pain and cramps, depression and anxiety, gastrointestinal symptoms, vitality, neuro-vegetative symptoms) was analyzed.
Results
In hypoPT patients 87% had serum calcium-levels within the target range. Serum-phosphate-levels and calcium-phosphate-product were within reference range in 95.7% of patients, or 100% respectively. The scores for pain and cramps and neuro-vegetative symptoms were significantly elevated in comparison with one (neuro-vegetative symptoms; $P=0.002$) or both (pain and cramps; $P=0.001$) control groups. No laboratory parameter correlated with patients' complaints after Bonferroni correction. In contrast, treatment with alfacalcidol or calcitriol significantly influenced results on different subscales ($P=0.002$ and $P=0.021$, respectively).
Conclusions
This study identified pain and cramps and neuro-vegetative symptoms as relevant areas of complaints in predominantly well controlled patients with hypoPT. Our data suggest that different active vitamin D agents may influence certain disease manifestations. The impact of different treatment regimen on clinical manifestations of hypoPT patients should be more intensively investigated.

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GP183

A novel mutation in the calcium sensing receptor GENE IN AN Italian family affected by autosomal dominant hypocalcemia

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The G protein-coupled calcium sensing receptor (CaSR), widely expressed on the surface of parathyroid chief cells and in the kidney, plays a central role in calcium homeostasis. Activating mutations of *CaSR* gene are responsible for autosomal dominant hypocalcemia (ADH), a rare disorder caused by hypocalcemia, hyperphosphatemia, hypercalciuria and inadequately low concentration of parathyroid hormone (PTH). In this study, we report a family affected by ADH. The proband, a 26 year-old Italian woman, was referred to our Department in 2011 for a mild asymptomatic hypocalcemia detected in 2009 during routine blood tests. Biochemical evaluation confirmed a mild hypocalcemia (mean value: 8 ± 0.26 mg/dl, normal range: 8.6–10.2), normal serum PTH (mean value 22 ± 5.57 pg/ml, normal range 8–40) and relative 24 h urinary calcium excretion (mean value: 171 ± 30.3 mg/24 h, normal range: <250). Instrumental evaluation excluded intracranic calcifications, kidney stones and nephrocalcinosis. Serum calcium of first-degree relatives showed hypocalcemia in her father (8.1 mg/dl) and brother (8.2 mg/dl), and normocalcemia in her mother (9.6 mg/dl). Genomic DNA of the proband and her family members was isolated from peripheral blood leukocytes and the entire coding region and exon-intron boundaries of the *CaSR* gene were directly sequenced. Mutational analysis revealed a novel heterozygous variant of the *CaSR* gene in the proband, leading to the substitution of serine to proline at codon 591 in exon 7 (S591P), localized in the *CaSR* extracellular domain where $>85\%$ of activating mutations occurs. All affected relatives carried the same alteration that was absent in her mother and in 100 chromosomes of unrelated healthy subjects. *In silico* tests, using Mutation Taster software that integrates data from different databases, predicted a probably deleterious effect of the detected variant. In conclusion, we identified a novel missense variant in the *CaSR* gene co-segregating with hypocalcemia.

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Pituitary/Growth Hormone & IGF Axis

GP184

Adrenal insufficiency induced by anti-PD-1/anti-PD-L1 therapy in patients with cancer: a series of cases

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Background
Immune checkpoint inhibitors like monoclonal antibodies targeting programmed death 1 receptor (PD1) or its ligand (PD-L1) have shown antitumor activity in many malignancies by enhancing immune response against cancer cells resulting in significant long-lasting responses. However, this therapy can induce endocrine immune-related adverse events (EirAEs). Thyroid dysfunction is a common EirAE, while adrenal insufficiency (AI) is very uncommon.
Objective
To report our experience on anti-PD1/anti-PD-L1-induced impairment of the hypothalamic-pituitary-adrenal (HPA) axis in cancer patients.
Results
Four patients (two males; mean age 55.5 (±7.6) years) with advanced cancer (3 non-small cell lung cancer (2 locally advanced and 1 metastatic) and one metastatic head and neck squamous cell carcinoma) were included. Three patients received anti-PD1 treatment (one combined with chemotherapy) and the other one was treated with anti-PD-L1 therapy plus chemotherapy. No one was under

steroid therapy. The clinical features of AI were: fatigue (all patients), nausea/vomiting (25%), low blood pressure (25%), hyperkalemia (25%), and hyponatremia (50%). All cases had low baseline serum cortisol levels at diagnosis [mean: 23.5(±34) nmol/l; range: 5–80; normal range (NR): 172–497)] with absence of response to cosyntropin stimulation test. Three out of 4 patients developed secondary AI due to isolated adrenocorticotropic hormone (ACTH) deficiency (ACTH <1.1 pmol/l; NR: 2–12), whereas 1 patient developed primary AI due to autoimmune adrenalitis (positive anti-adrenal antibodies, ACTH: 237 pmol/l). All patients had a normal pituitary MRI and abdominal CT scan. Baseline serum concentrations of the rest of pituitary hormones (TSH, LH, FSH, GH, and PRL) as well as fT4 and IGF-1 were within the normal range in all cases. Patients were treated with replacement doses of hydrocortisone. All patients had to stop immunotherapy temporarily, but in 3 of them, it was reintroduced after a median of 41(±13.5) days. After 7.5±6.4 months (range: 3–18) of follow up, all patients remained with steroid hormone replacement therapy. Interestingly, 2 patients had a complete tumor response despite the advanced stage of the disease; one remained with stable disease after 12 months of follow-up and only one patient progressed 8 months after starting immunotherapy.

Conclusion

Cancer patients treated with anti-PD1 or anti-PD-L1 therapy can develop a persistent immune-related primary or secondary adrenal insufficiency. Isolated ACTH deficiency is the most frequent alteration in our series. In the primary failure, an autoimmune mechanism is suggested. Interestingly, half of these patients achieved a complete response.

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GP185

Long-term treatment with metyrapone in four patients with Cushing's disease

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Introduction

Cushing's disease (CD) is a severe disease, associated with an increased rate of comorbidities and mortality. Remission rate after surgery of pituitary tumor, is around 78%. Relapse occurs in 13% of patients within 10-years after surgery. According to guidelines, patients with unfeasible or non-curative surgery, require additional treatment, including medical therapies. Metyrapone, inhibits 11ß-hydroxylase enzyme, blocking the final step of cortisol synthesis in adrenal cortex. Daily dosage ranges from 250 to 6000 mg. An international European phase III/IV study (PROMPT) started in 2015 to evaluate efficacy and safety of metyrapone in endogenous Cushing's syndrome. Metyrapone was individually titrated during the first 3 months. An extension period of 6 months was proposed to patients who normalized mean urinary free cortisol (mUFC) or did not exceed 2-fold the normal upper limit (ULN =165 nmol/24 h). In Belgium, four patients were treated during 9 months in PROMPT study and benefited from further therapy with metyrapone through a medical need program. Results: Three women and one man with CD, previously treated by pituitary surgery for 3 of them and/or medical treatment, were controlled during the trial with daily doses between 500 and 5750 mg. Centralized UFC measurements (LC–MS/MS method) showed a baseline mUFC value of 768 nmol/24 h [range: 291–1244] reduced under ULN after 3 and/or 9 months of treatment in 3 of them. Baseline mUFC of last patient decreased by more than 50% after 9 months therapy to 235 nmol/24 h. ACTH remained unchanged after the first 3 months of therapy, except for the patient who needed 5750 mg/day of metyrapone (3.2-fold ACTH increase). The baseline mUFC was also the highest in this last patient. Despite a controlled disease with metyrapone, the fourth patient decided after 21 months of treatment to undergo bilateral adrenalectomy. The three others were still controlled after 24 months. Clinically, fatty deposits disappeared in 3 patients out of 4 (75%) and bruising disappeared in 2 patients out of 2 (100%). Regarding safety, patients experienced each 1 to 4 mild to moderate AEs during the 9 months of PROMPT study: nausea, fatigue, tiredness, dizziness, migraine, loss of appetite and arthralgia. Tolerance was still good during extension period after the 9 months study. No hirsutism or acne was observed in women. Conclusion: Metyrapone showed good efficacy and tolerance in long term management (up to 24 months) of 4 patients with CD.

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GP186

Primary posterior pituitary tumors: a unique neoplasm with hight morbidity

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Background

The 2017 World Health Organization classification of pituitary tumors established that, pituicytoma, granular cell tumor of the sella (GCT) and spindle cell oncocytoma (SCO) are posterior pituitary tumors (PPT). These lesions are non-neuroendocrine and low-grade neoplasms of the sellar region presenting with mass effect symptoms. Their clinical manifestation, hormonal profile and radiological findings are indistinguishable from non-functioning pituitary adenomas (NFPA). Recent data suggests that these three tumors could have a common origin from the pituicytes.

Aim

To evaluate a retrospective multicenter study of 15 patients with histological diagnosis of PPT.

Results

Our series included 6 pituicytomas, 3 GCT and 6 SCO. Mean age at diagnosis was 54.2 years old (range 30–74) and 11 patients were female. The most common symptoms of clinical presentation were visual defects (40%), amenorrhea (20%) and sever hyponatraemia (20%). One case had hypercortisolism symptoms. Hormonal assessment showed hyperprolactinemia (40%), hypopituitarism (33%) and ACTH dependent hypercortisolism in one patient. No patient had diabetes insipidus (DI). MRI showed sellar/suprasellar masses with median size of 24.5 mm (±10.3), chiasmatic compression in 46% and cavernous sinuses infiltration in 13% of the patients. Fourteen patients underwent surgery (one patient died before intervention and diagnosis was made by previously biopsy). In 10 patients transphenoidal approach was performed while craniotomy was chosen in 4 cases. Serious bleeding during surgical procedure occurred in 3 cases (20%) and one of them died due to hemorrhage in the early postsurgical period. After surgery 8 patients had hypopituitarism (61%) and 5 patients (38%) developed DI. Complete resection was achieved in 8 cases and residual tumor persisted in the remaining 5 patients. A second intervention was performed in 3 cases (20%). The pathological evaluation of pituitary specimen in the patient with *Cushing's disease*, revealed a concomitant corticotropes hyperplasia and a GCT. *Cushing's disease* persisted after three interventions in this patient, radiotherapy and adrenolytic agent were also prescribed.

Conclusion

PPT are usually misdiagnosed as NFPA because of their clinical and imaging characteristics. However, the behave more aggressive than NFPA and the perioperative complications such as intra-operative bleeding, hypopituitarism, DI and incomplete resection are common.

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GP187

Erdheim-chester disease presenting with hypopituitarism and diabetes insipidus

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Introduction

Erdheim-Chester disease (ECD) is a rare and aggressive form of non-Langerhans cell histiocytosis (n-LCH). Its etiology is unknown, but recently, BRAFV600E (a

proto-oncogene) has been found in more than 50% of cases. This may play a part in chronic uncontrolled inflammation, which is an important aspect of disease pathogenesis.
Case report
A 42-year-old woman complained of generalized weakness, polyuria, and secondary amenorrhea. Biochemistry results revealed elevated plasma osmolality (309 mOsm/l), relatively low urinary osmolality (131 mOsm/l), and no serum AVP. Further results showed that both cortisol (4.3 μg/dl) and ACTH (9.1 pg/ml) were at the lower limit of the normal range. The patient's free T4 level was low (0.60 ng/dl), while her TSH level was within the normal limits. The prolactin level was increased (92.33 ng/ml), and estradiol was not detected. LH and FSH were low (<0.10 and 0.71 mIU/ml, respectively). The IGF-1 level was also low (62 ng/ml). A hormonal provocation test (CRH, TRH, GRH, and LH-RH) revealed hypothalamic panhypopituitarism. We performed cranial magnetic resonance imaging, which showed signal loss in the posterior pituitary region on T1-weighted images. Furthermore, space-occupying lesions were found in the hypothalamus, brainstem, and temporal lobes when Gad-enhancement was used. Positron emission tomography revealed slightly increased uptake activity in both peripheral lung fields. Video-assisted thoracoscopic surgery was performed for diagnostic purposes to obtain a tissue biopsy. Immunohistochemistry of the lung lesion demonstrated the presence of n-LCH markers, positivity for CD68, and negativity for S-100 protein and CD1a. Bone scintigraphy revealed symmetrically increased osteoblastic activity in the lower limbs. We reached a diagnosis of ECD with pan-hypopituitarism and central diabetes insipidus. BRAF mutation was negative in Sanger sequencing. The patient was treated with 12.5 μg of 1-desamino-8-D-arginine vasopressin (DDAVP) per day for diabetes insipidus. We started regular hydrocortisone 10 mg per day, followed by levothyroxine. For the ECD itself, she was first treated with 40 mg of prednisolone per day, and the tumors slightly decreased in size. However, the dose was tapered rapidly because of worsening of diabetes. The treatment was then commenced with interferon α, but the tumors did not decrease in size. We discontinued the treatment because it induced liver damage.
Conclusion
We present a rare case of ECD that presented with hypopituitarism and diabetes insipidus and involved several organs, including the cerebrum, bones, and both lungs.
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GP188

Growth disorders in paediatric survivors of hematopoietic stem cell transplantation after chemotherapy-only conditioning- the experience of a single center
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Objective
The reported incidence of growth disorders in hematopoietic stem cell transplantation (HSCT) recipients ranges from 20 to 80% and it was usually described in patients that were given total body irradiation (TBI) in the conditioning regimen. Because the effect of chemotherapy-only conditioning is less clear, we investigated the frequency of growth failure in our series of children treated with HSCT for different disorders without TBI as part of the conditioning protocol.
Material and method
We compared height and IGF-I *z*-scores in 22 HSCT survivors and 16 healthy subjects matched for age and sex. Short stature was defined as height *z*-score < -2 S.D.
Results
We identified 4 patients with short stature. HSCT recipients had a higher frequency of short stature (18.83% vs 0%, $P=0.027$) compared to the control group. Patients transplanted for beta-thalassemia major were more likely to have short stature compared to patients with non-malignant hematologic diseases and malignant hematologic/non-hematologic disorders (100% vs 16.66% and 7.69%, respectively, $P=0.04$). The longer time elapsed from HSCT ($P=0.012$) and allogeneic compared to autologous grafting ($P=0.019$) were associated with a higher prevalence of growth failure in our study. HSCT survivors had lower mean height *z*-score ($P=0.029$) and lower body mass index *z*-score ($P=0.027$) compared to controls. Multivariate analysis revealed that allogeneic HSCT recipients had lower mean height *z*-score ($P=0.002$) and lower mean IGF-I *z*-score ($P=0.006$) compared to auto-HSCT recipients and controls.
Conclusion
Almost 20% of the patients in our cohort presented short stature despite the fact that they received chemotherapy-only conditioning, emphasizing the need for long-term surveillance of growth even in this group of patients that were not exposed to TBI.
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GP189

Association of IGF1 receptor autoantibodies with height and body size
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Objective
Insulin-like growth factor 1 (IGF1) has a crucial role in growth and metabolism. A specifically designed autoantibody (aAb) assay against the IGF1 receptor (IGF1R-aAb) is able to detect IGF1R-aAb in serum. As the IGF1R has shown involvement in many functional pathologies (e.g. in the Laron syndrome), we aimed to investigate the role of IGF1R-aAb in a large population-based cohort of middle-aged volunteers and their potential effects on anthropometric, osteological and metabolic characteristics.
Methods
Clinical and biochemical parameters of 966 volunteers (531 female and 435 male) of the BioPersMed cohort (*Bio*markers in *Pers*onalized *Med*icine, Medical University Graz) were analysed to identify putative differences between IGF1R-aAb positive (binding index >3 – times above background) and control subjects. Laboratory data in combination with DXA-derived measurements of bone density, dimensions and body composition allowed a detailed insight into the relation of IGF1R-aAb with biomarkers (body height and composition, hormones and metabolic factors). Unpaired 2 tailed *T*-test was used to test for statistical significance.
Results
Mean age of the cohort was 57.7 years ± 8.1 years for women and 58.4 years ± 9.0 years for men. IGF1R-aAbs were identified in 6.0% of all volunteers (7.6% female and 5.2% male). IGF1R-aAb positive volunteers showed significantly different bone density ($P=0.001$), body composition ($P=0.012$) and a significant increase in body height [+4.1 cm in men ($P=0.002$) and +1.6 cm in women ($P=0.1$)], with a more pronounced effect in men. There was no difference in age or BMI between the groups.
Summary and conclusions
IGF1R-aAbs are relatively prevalent in healthy adult humans and may affect body height by modulating bone growth. However, their origin, regulation, and relation to hormonal and metabolic pathways have not yet been fully clarified. Therefore, research and monitoring of IGF1R-aAb prevalence before puberty and during lifetime of women and men is a compelling approach but the mechanisms around IGF1R- aAbs and their potential effects remains to be elucidated.
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GP190

Insulin sensitivity improves after disease control in acromegaly irrespective of treatment modality and despite an increase in intrahepatic lipid content: data from an investigator-initiated prospective trial

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Background
Active acromegaly induces insulin resistance despite a lean phenotype, both of which reverse by curative surgery. The impact of somatostatin analogue treatment on insulin sensitivity is less certain and may be offset by its anti-lipogenic effects.
Aim
To study insulin sensitivity, body composition and extopic lipid content in newly diagnosed patients with acromegaly before and $\geq$6 months after successful surgical or medical treatment.
Patients and methods
21 patients with acromegaly underwent a hyperinsulinemic, euglycemic glucose clamp (HEC), dual x-ray absorptiometry (DXA) scan, and MR spectroscopy to quantify lipid content in liver (IHL) and muscle (IMCL).
Results
10 patients were controlled by surgery alone and 11 patients were controlled by a somatostatin analog (SA). Mean $\pm$ s.e. serum IGF-I levels (μg/l) before and after treatment were 696 $\pm$ 90 and 221 $\pm$ 33 with no treatment-specific difference either before ($P=0.75$) or after treatment ($P=0.11$). Insulin sensitivity assessed by mean $\pm$ SE glucose infusion rate (GIR) during the HEC (mg/kg per min) increased after treatment ($P=0.001$) regardless of modality ($P=0.505$) [GIR: 3.3 $\pm$ 0.4 (before) vs. 4.7 $\pm$ 0.5 (after)]. Disease control induced a 17% increase in total body fat ($P=0.001$) and 8% decrease in lean body mass ($P<0.000$). IHL (% CH2/water) increased after disease control, regardless of modality: 2.8 $\pm$ 0.6 (before) vs. 6.7 $\pm$ 2.2 (after) ($P=0.04$). IMCL did not change in either group.
Conclusions
1) The improvement in insulin sensitivity and change in body composition after disease control of acromegaly appear independently of treatment modality, 2) Our data extend and support the notion that IHL is a GH target, 3) Acromegaly and its treatment exemplifies that insulin sensitivity and body composition do not always walk hand in hand.

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GP191

Ectopic Cushing's syndrome secondary to medullary thyroid carcinoma with apparent signs of hypercortisolism: a case report

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Introduction
Ectopic ACTH syndrome (EAS) is a rare cause of Cushing's syndrome. EAS is most frequently caused by bronchial carcinoid tumor or small cell lung cancer. Medullary thyroid carcinoma (MTC) is a rare source of EAS, as reported in this case.
Case report
A 65-years-old-female with back pain and weight gain referred to our outpatient clinic with determined signs and symptoms of hypercortisolism. She had arterial hypertension, her sister had operated for thyroid malignancy. The significant findings were; centripedal obesity, plethora, muscle weakness, hypertension, overt diabetes and osteopenia. Laboratory tests were as follows: repeated 24-hour urinary free cortisol (UFC) excretions:900 and 978 μg/dl (n 36–137 /24h); midnight salivary cortisol:1.82 and 2.71 μg/dl (n <0.2 μg/dl); midnight plasma cortisol: 17.73 and 27.24 μg/dl (n <7,5 μg/dl), 1 mg dexamethasone supression test (DST): 17.56 μg/dl, 2 day 2 mg DST: 13.2 μg/dl.The high levels of ACTH (86.5 and 84.1 pg/ml), non-supressed 8 mg DST (18.03 μg/dl), insufficient increase serum cortisol and ACTH levels post CRH-stimulating testing and no mass on pitutiary MRI scanning confirmed ectopic ACTH syndrome. Imaging studies performed for tumor localization, showed a solid thyroid nodule, 20× 18 mm in diameter. Fine needle aspiration(FNA) of the thyroid nodule revealed MTC and calcitonin level in wash-out fluid from FNA was very high (12311 pg/ml), similar with plasma level (3068 pg/ml). Functional PET imaging with 68-Ga DOTATATE demonstrated pathological uptake at right thyroid lobe and right parapharyngeal area. A total thyroidectomy and bilateral, central neck dissection were performed, histology confirming MTC with immunohistochemistry-staining positive for calcitonin, CEA and ACTH. The carcinoma metastases were detected at lymph nodes localized at right level 2 and right parapharyngeal area. Postoperative 24-h UFC (368 μg/dl), 1 mg DST (4.8 μg/dl) and plasma ACTH (40.1 pg/ml) levels revealed uncontrolled hypercortisolism. The measurements of serum calcitonin and CEA were planned three months after surgery to detect the presence of residual disease.
Conclusion
Nearly 50 cases have been reported about EAS induced by MTC; however, to the best of our knowledge this is the first case in the literature from Turkey. Mortality in MTC with EAS due to complications of hypercortisolism is 50%. Therefore, management of Cushing's syndrome in MTC is very important. Surgical removal of MTC is recommended to control CS, but management is limited to debulking metastatic disease.

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GP192

A case series of endocrine immune-related adverse effects of checkpoint inhibitors

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Background
With the increasing use of cancer immunotherapies in advanced solid organ and hematologic malignancies, endocrinologists are beckoned to manage endocrine complications with unique presentations and natural history in the already challenged oncology patient. We describe four patients illustrating the multifarious endocrine adversities of checkpoint inhibitors.
Cases
Patient 1 is a 35-year old male with refractory Hodgkin's lymphoma, previously euthyroid and euglycemic. He was treated with nivolumab for three months before developing profound antibody-negative hypothyroidism (TSH 71.8 mIU/ml, fT4 <0.3 ng/dl), nephrotic syndrome (20 g proteinuria/d), insulin-requiring anti-GAD positive diabetes mellitus and positive tissue transglutaminase antibodies (pending duodenal biopsy), after six cycles of treatment. He presented a palpable hypoechoic goiter with increased vascularity. Patient 2 is a 76-year old male with metastatic melanoma with rapidly declining to suppressed TSH levels, fT4×3ULN and fT3×2ULN after the second infusion of nivolumab. He had a palpable hypoechoic thyroid gland, with increased vascularity. Thyroid-stimulating immunoglobulins were undetectable while anti-TPO were mildly positive. Within six weeks, he precipitously reverted to hypothyroidism (TSH 85 mIU/ml) and his thyroid gland regressed to marked atrophy. Patient 3 is a 59-year-old male with metastatic melanoma, who was switched to pembrolizumab after developing hypophysitis with ACTH (2 pg/ml) and prolactin (<1.0 ng/ml) deficiencies in addition to diabetes insipidus following four infusions of ipilimumab. He maintained intact thyroid, gonadal and GH axes while continuing pembrolizumab for two years, with stable disease. Patient 4 is a 49-year-old male with relapse of Hodgkin's lymphoma 4.5 years after autologous stem cell transplantation. He was previously euthyroid, but developed antibody-positive hypothyroidism after 4 cycles of pembrolizumab, demonstrating a hypoechoic 'honeycomb' gland. His TSH reached a peak of 37.88 mIU/ml, with corresponding levels of fT4 at 0.36 ng/dl (normal 0.7-2) and fT3 at 1.26 pg/ml (normal 2–4.4), indicating a possible central component to the hypothyroidism. The thyroid gland was barely discernible by ultrasound a year later.
Conclusion
The patterns of thyroid and pituitary dysfunction observed with checkpoint immunotherapy challenge our current understanding of 'thyroiditis' and 'hypophysitis'. Endocrinopathies resulting from these agents are common, mostly permanent and potentially life threatening, calling for regular monitoring, prompt management and coordination of care, so that cancer treatment may be safely continued.

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GP193

Hypophysitis due to immune checkpoint blockade: rising numbers.

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Hypophysitis is one of the immune-related adverse events of immune checkpoint blockade. This complication is potentially dangerous, mainly because of the insidious development of a life-threatening hypocortisolism. Unnecessary morbidity or mortality in an oncological responder may be the result. The number of patients treated with immune checkpoint inhibitors increases rapidly, due to the expansion of indications and trials. Moreover, the introduction of combination schedules leads to more adverse events.PD-1 inhibitors induce hypophysitis in an estimated 1%, the CTLA-4 inhibitor ipilimumab in approx. 5–10% and for the ipilimumab plus PD-1 inhibitor combination percentages up to more than 10% are reported. Caregivers need to be aware of this complication, and should coordinate their protocols accordingly. During the last 5 years we have encountered 26 patients with an immune checkpoint inhibitor-related hypophysitis, of which 11 patients in the last year alone. Ipilimumab is the main cause, but due to the large number of patients treated, monotherapy with PD-1 blockers is represented as well. The time of occurrence of a hypophysitis after starting immunotherapy was 5–18 weeks for Ipilimumab and 13–57 weeks for PD-1 inhibition (Pembrolizumab or Nivolumab). In 2 patients the hypophysitis occurred more than 1 year after the start of immunotherapy, and even after the discontinuation of immunotherapy, illustrating the need for long-term surveillance. The pattern of endocrine dysfunction was typical, failure of especially the adrenal axis (24 out of 26), accompanied by failure of the gonadal and thyroid axis (18 out of 26). The gonadal and thyroid axis showed recovery of function in about half of the cases. MRI abnormalities were minor, mostly in the form of a short-lived infiltrate in the sella without a large mass effect, and especially present in the Ipilimumab group (7 out of 12, as far as a simultaneous MRI is present). In 9 patients the hypophysitis was preceded by a thyroiditis, mostly during treatment with PD-1 inhibitors. Glucocorticoid substitution alone could suffice, without the need for high-dose steroid therapy, which was only applied in the first index patient in 2012, according to the guideline at that time. Based on our current experience the role for high-dose steroid therapy in immune checkpoint inhibitor-related hypophysitis is less prominent than recommended in the recent ESMO Clinical Practice Guidelines.

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Pituitary Basic

GP194

Olfactory marker protein regulates prolactin secretion and production by modulating Ca^{2+} and TRH signaling in lactotrophs

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Olfactory marker protein (OMP) is a marker of olfactory receptor-mediated chemoreception, even outside the olfactory system. Here, we report that OMP expression in the pituitary gland plays a role in basal and thyrotropin-releasing hormone (TRH)-induced prolactin (PRL) production and secretion. We found that OMP was expressed in human and rodent pituitary glands, especially in PRL-secreting lactotrophs. OMP knockdown in GH4 rat pituitary cells increased PRL production and secretion via extracellular signal-regulated kinase (ERK)1/2 signaling. Real-time PCR analysis and the Ca^{2+} influx assay revealed that OMP was critical for TRH-induced PRL secretion. OMP-knockout mice showed lower fertility than control mice, which was associated with increased basal PRL production via activation of ERK1/2 signaling and reduced TRH-induced PRL secretion. However, both *in vitro* and *in vivo* results indicated that OMP was only required for hormone production and secretion because ERK1/2 activation failed to stimulate cell proliferation. Additionally, patients with prolactinoma lacked OMP expression in tumor tissues with hyperactivated ERK1/2 signaling. These findings indicated that OMP plays a role in PRL production and secretion in lactotrophs through the modulation of Ca^{2+} and TRH signaling.

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GP195

Filamin A (FLNA) phosphorylation inhibits SSTR2 signal transduction in GH-secreting pituitary tumor cells

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Despite the increasing evidence on the relevance of the actin binding protein filamin A (FLNA) in determining an efficient intracellular response to somatostatin analogs (SSA) in pituitary tumors, there is a gap in the knowledge on the mechanisms regulating FLNA itself. FLNA is phosphorylated by PKA on Ser^{2152} located in a FLNA region crucial for SST2 or partner proteins binding. Although cAMP/PKA pathway plays a crucial role in GH-secreting tumors pathogenesis, the biological relevance of FLNA phosphorylation is unknown. Aim of this study is to investigate in rat and human GH-secreting pituitary tumor cells ($N=3$) the impact of cAMP pathway activation and SSA stimulation on FLNA phosphorylation and the consequences on SST2 function. We found a PKA-mediated increase (about 2-fold) and SST2 agonist-induced decrease (-50%) of FLNA Ser^{2152} phosphorylation (P-FLNA) in GH3, GH4C1 and primary somatotroph tumor cells. By transfecting phosphomimetic (S2152D) and phosphodeficient (S2152A) FLNA mutants in GH3 cells, we found that S2152D FLNA abolished the antiproliferative effects exerted by BIM23120 in wild type or S2152A FLNA transfected cells ($-32\pm13\%$ and $-21\pm3\%$, respectively, $P<0.05$ vs basal). Moreover, BIM23120 increased caspase activity in wild-type and S2152A FLNA transfected cells ($+39\pm13\%+28\pm9\%$, respectively, $P<0.05$ vs basal), but not in S2152D FLNA transfected cells, suggesting a negative effect of FLNA phosphorylation on SST2 signal transduction. Co-immunoprecipitation and immunofluorescence analysis revealed that S2152D FLNA is able to bind SST2 on the plasma membrane both in basal conditions and after SST2 activation, whereas wild-type and S2152A FLNA are recruited to SST2 after 5 min of agonist stimulation. We can hypothesize that FLNA phosphorylation impair the ability of FLNA to bind proteins involved in SST2 signaling without affecting, or even increasing, its ability to bind SST2. In conclusion, our data suggest that cAMP pathway activation abolishes the ability of FLNA to function as scaffold for SST2 signal transduction by increasing FLNA phosphorylation, whereas SST2 activation induces FLNA dephosphorylation in a positive auto-regulatory loop. Since SST2 functions are regulated by FLNA, modulation of P-FLNA might suggest new pharmacological strategies for SSA resistant pituitary tumors as well as a new biomarker for tumor responsiveness to SSA.

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GP196

E-cadherin expression is associated with the response to somatostatin analogues in patients with acromegaly

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Aim

To assess whether E-cadherin expression levels in somatotropinomas were associated with the response to somatostatin analogues (SSAs) therapy in patients with acromegaly.

Methods
In this retrospective study, 56 acromegaly patients that underwent transsphenoidal surgery were evaluated. All patients were treated preoperatively with SSAs (octreotide or lanreotide) for at least 6 months. Responsiveness to SSAs was evaluated by percent IGF-1 reduction after 3 and 6 months of treatment. Quantitative PCR was used to measure the expression of somatostatin receptors (SSTR1-SSTR5) and dopamine receptors (DRD1-DRD5). The expression of E-cadherin was evaluated by immunohistochemistry. Clinical and pathological variables were collected to evaluate potential associations between these variables and E-cadherin expression.
Results
28 of the somatotropinomas examined were found negative for E-cadherin. The remaining adenomas displayed moderate (10) or strong (18) immunoreactivity for E-cadherin and were analyzed as one single group. No statistically significant differences were observed between E-cadherin negative and positive adenomas regarding age, tumor invasion and GH and IGF1 levels at diagnosis. E-cadherin negative somatotropinomas were larger and more prevalent in women than in men. Almost all E-cadherin negative somatotropinomas were sparsely granulated adenomas. The IGF-1 per cent reduction after 3 and 6 months of SSAs treatment was significantly in E-cadherin negative adenomas compared with moderate/high E-cadherin adenomas. At 3 months of treatment, the median IGF-1 per cent reduction for adenomas negative for E-cadherin was 4.1 and 44.2 for adenomas positive por E-cadherin. At 6 months of treatment, the median IGF-1 per cent reduction for adenomas negative for E-cadherin was 8.9 and 49.8 for adenomas positive for E-cadherin. E-cadherin negative adenomas displayed lower SSTR1 and DRD4 expression levels.
Conclusions
In our series, a poor response to treatment with SSAs in patients with acromegaly is associated with absence of E-cadherin accumulation in somatotropinomas.

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GP197

Efficacy of pharmacological USP8 inhibition in human Cushing's disease tumours *in vitro*

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The tumorigenesis of Cushing's disease is characterized by somatic mutations in the USP8 gene in almost half of the cases. USP8 encodes for ubiquitin specific protease 8, a deubiquitinase that rescues proteins involved in the regulation of ACTH synthesis in corticotroph cells. In the present study we tested the antisecretory and antiproliferative efficacy of a commercially available specific USP8 inhibitor (IC50 3.1 μM USP8; >90 μM USP7) in immortalized murine corticotroph tumour AtT-20 cells and human corticotroph tumours in primary cell culture ($n=11$). The USP8 inhibitor decreased POMC transcription and promoter activity and ACTH secretion in a dose response manner starting from 10 nM (% suppression at 1 μM 58±2, 53±12 and 59±7 respectively). Knocking down USP8 abolished the inhibitory effect on POMC promoter activity, confirming the specificity of the targeted treatment. Treatment of the human corticotroph tumours *in vitro* decreased ACTH secretion beyond the arbitrarily set cut-off of 20%in all cases at 1.5–3 μM concentration (% suppression 33±15 and 44±17 respectively), 9 out of 11 cases at the 1 μM (% 34±15) and 7 out of 11 at the 0.1 μM (% 24±16). No toxicity was observed in any of these concentrations. In AtT-20 cells the USP8 inhibitor (1 μM) decreased cell number (% suppression 35%±1) without affecting cell volume and without cytotoxicity. The treatment decreased cell viability at 1 μM (but not at lower concentrations; % suppression 30±3). No changes in the apoptosis markers PARP and cleaved caspase 3 were observed under these conditions. All human corticotroph tumours responded to 3 μM by decreasing cell viability (% suppression 46±18) and 6 out of 11 to 1 μM treatment (% 30±24). Co-treatment with EGF, an ACTH secretagogue whose receptor is the best characterized target of USP8, in EGFR-overexpressing AtT-20 cells shifted the antiproliferative and antisecretory response to the USP8 inhibitor (% suppression 36±3 vs 27±2 and 64±6 vs 57±7 at 1 μM respectively), indicating that in part the effect of USP8 inhibition is mediated via its inhibitory crosstalk with the EGFR signalling. Altogether these data show that pharmacological USP8 inhibition can effectively suppress ACTH synthesis *in vitro* without accompanying cytotoxicity and indicate its potential for the management of ACTH hypersecretion in Cushing's disease.

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GP198

Ubiquitin specific peptidase 8 (USP8) in human corticotroph pituitary tumors- possible targets and mode of action

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Recently, somatic, heterozygous mutations in the gene encoding the deubiquitinase USP8 have been identified in 30–60% of corticotroph tumors. These mutations were found to hinder binding of 14-3-3 proteins, increasing its deubiquitinating activity. One substrate is Epidermal Growth Factor Receptor (EGFR), USP8 triggers EGFR recycling and increased EGFR signaling. However, tumors harboring mutations in USP8 are smaller than WT tumors, raising the debate if EGFR, as a potent growth factor, is the only substrate of USP8 in these tumors. We aimed to identify putative USP8 targets that might explain the tumorigenesis and increased ACTH secretion of these cells. We performed a literature search to identify putative USP8 targets, revealing several proteins with deregulated expression associated with corticotroph tumors that might be the result of increased USP8 deubiquitination (e.g. the transcription factors TR4 and CREB). Candidates were analyzed by IHC for their expression levels on FFPE tissue (pituitary tumors: corticotrophs ($n=85$), functionally inactive ($n=19$), somatotrophs ($n=12$) and normal pituitary glands ($n=5$)). We further metabolically labeled, transiently transfected the murine corticotroph cell line AtT-20 with USP8 WT or mutant plasmids and performed Tandem-Ubiquitin-Binding-Entity (TUBE)-assays, followed by nanoLC-MS/MS analysis to identify changes in poly-ubiquitinated protein abundance. Of the 10 proteins analyzed by IHC, 3 had an altered expression pattern between USP8 WT and mutated tumors, namely $p27/^{kip1}$ (mean expression: 1±0.7 vs 0.4±0.6 ($P=0.003$)), AVPR1b (mean expression: 0.8±0.6 vs 0.3±0.4 ($P=0.0045$)), phospho-CREB (mean expression: 0.7±0.7 vs 1.3±0.9 ($P=0.0165$)). TUBE assays revealed an increased de-ubiquitination of Small Ubiquitin-Like Modifier 3 (SUMO3) in $USP8^{mut}$ transfected cells, suggesting co-occurrence of another post-translational protein modification. In conclusion, these results suggest a much more complicated mechanism of action of the identified mutations in USP8, with sumoylation adding another dimension to the regulation of a USP8 mediated equilibrium between degradation and recycling.

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GP199

Prominent expression of MAX and MEG3, despite lack of mutations in MAX, suggest a potential role for 14q genes in pituitary adenomas

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Pituitary adenomas (PA), as well as pheochromocytomas and paragangliomas, are neuroendocrine tumors that arise from cells derived from the pituitary, adrenal and extra-adrenal nervous system, respectively. Recent studies have identified a growing series of susceptibility genes for these pathologies. Some genes may be associated with the development of both types of pathologies, as it is the case for succinate dehydrogenase complex genes, while, PAs have not been reported to date in patients harboring the most recently discovered pheochromocytomas and paraganglioma susceptibility genes, such as MAX, the MYC-associated factor X gene. Interestingly *MAX* is able to form heterodimers with MYC, an oncogene implicated in cell proliferation and apoptosis, which has been recently identified as a biomarker of aggressiveness in non-functioning Pas (NFPAs). Thus, to explore if *MAX* and/or *MEG3* (an imprinted gene located close to MAX, which arose as a marker of uniparental disomy in *MAX*-mutated patients) are associated with pituitary tumorigenesis, we analyzed *MAX* genomic sequence [by denaturing high-performance liquid chromatography (dHPLC)] in a cohort of 141 PA samples [71 NFPAs, 40 somatotropinomas, 19 corticotropinomas, 10 prolactinomas and 1 gonadotropinoma], together with the analysis of MAX and MEG3 expression (by qPCR) and/or methylation status (using bisulfite modification and methylation specific PCR). These analyses revealed that *MAX* and *MEG3* were substantially expressed in the different types of PA, wherein they displayed a tumor type-specific expression pattern: expression levels were significantly higher in somatotropinomas compared with NFPAs. Specifically, detectable MAX and MEG3 expression levels was present in 100% and 97% of somatotropinomas, 93% and 81% of NFPAs, 90% of corticotropinomas, and in 60% and 100% of prolactinomas, respectively and both were expressed in the gonadotropinoma. Interestingly, *MAX* and *MEG3* expression levels were directly correlated in this cohort of PAs, an observation that also tended to arise independently in somatotropinomas and NFPAs ($p=0.07$ and 0.08, respectively). Remarkably, none of the PA samples presented *MAX* mutations in dHPLC and sequencing analyses, nor displayed significant alterations in the methylation status of the CpG sites of *MAX* and *MEG3* genes examined. Altogether, our results show that mutations in *MAX* gene do not seem to play a relevant role in pituitary tumorigenesis in this cohort of patients. However, *MAX* and *MEG3* are significantly expressed, suggesting that the study of their functional role in pituitary pathophysiology could represent an interesting avenue for the identification of novel biomarkers and/or therapeutic targets in these pathologies.

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GP200

Pharmacological characterization of somatostatin receptor subtype 3 as a potential strategy to treat non-functioning pituitary adenomas

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Non-functioning pituitary adenomas (NFPAs) represent the most common type of pituitary adenomas. NFPAs are mostly macroadenomas (>1 cm) at diagnosis and, despite their lack of functional hormone hypersecretion, are associated to severe comorbidities related to mass effect (i.e. headaches, visual defects and hypopituitarism). Transsphenoidal surgery is the mainstay of NFPAs treatment, although it is often not definitive, mainly due to the invasion of neighboring intracranial structures precluding complete resection. Unfortunately, there are no medical treatments currently approved or recommended to manage NFPAs. Indeed, somatostatin analogs (SSAs), commonly used to treat functioning pituitary adenomas, have been largely ineffective in NFPAs, which might be explained by the limited expression of the main targets for these SSAs, i.e. somatostatin-receptor subtypes 2 (sst2) and 5 (sst5). However, since it has been previously demonstrated that NFPAs present a predominant expression of sst3, the main objectives of this study were: 1) to perform a comprehensive characterization of the expression pattern of sst3 in NFPA and normal-pituitary (NP) tissues (by qPCR and IHC); and, 2) to determine the functional role of sst3 in NFPA by analyzing different functional endpoints (i.e. cell-viability, apoptosis, chromogranin-A secretion, mRNA expression and intracellular signaling pathways) in primary NFPA cell-cultures in response to selective sst3 agonists and antagonists. Our results demonstrate that sst3 is the most abundantly expressed sst-subtype in NFPAs ($n=71$), being also significantly overexpressed in NFPAs compared to NPs ($n=12$) and functioning pituitary adenomas like GHomas ($n=63$) and ACTHomas ($n=17$). Treatment with sst3-agonists reduced cell viability and chromogranin-A secretion, while increasing apoptotic rate in primary NFPA cell-cultures. These inhibitory effects of sst3-agonists were completely reversed by specific sst3-antagonists, confirming the specificity of the effects observed. Interestingly, our data revealed the existence of two distinct subgroups of NFPAs that responded differentially (responsive vs. unresponsive) to treatment with sst3-agonists in terms of reduction in cell viability, being sst3 expression levels higher in responsive NFPAs. Further analysis revealed that the effects of sst3-agonists might be mediated by the inhibition of MAPK-pathways, as suggested by reduced phosphorylation levels of ERK1/2 and JNK. Altogether, our study provides novel data strongly supporting that sst3 plays a relevant functional role in the pathophysiology of NFPAs, and suggests that pharmacological treatments targeting this receptor could be a promising therapeutic alternative for these tumors.

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GP201

Epigenetic and post-transcriptional regulation of the *SSTR5* gene in somatotropinomas

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The somatostatin receptor 5 (sst5) and its truncated splicing variants (sst5TMD5, sst5TMD4) are considered putative biomarkers that can predict pharmacological response or aggressiveness in several endocrine-related pathologies, such as acromegaly. sst5 is encoded by a gene, *SSTR5*, that lacks introns within its coding sequence, and hence, the splicing variants identified are generated by non-

canonical splicing events. However, the mechanisms underlying their genesis and regulation are still to be fully elucidated. Recent analyses of *SSTR5* gene structure revealed the existence of a natural antisense transcript, named *SSTR5-AS1*, which overlaps with *SSTR5* and encodes an intergenic long non-coding RNA that may be involved in the regulation of *SSTR5* expression and processing. Likewise, recent studies indicate that DNA methylation within genic regions could influence exon inclusion and alternative splicing. Accordingly, in this study we have implemented pilot *in silico* analyses of the human *SSTR5* and *SSTR5-AS1* genes to explore the existence of CpG islands (high density CG regions susceptible to be methylated), located at their promoters, and, most interestingly, within their coding regions. Our ultimate goal was to ascertain if these processes could contribute to the regulation of the expression of *SSTR5* and the generation of its variants in somatotropinomas. Firstly, we measured the mRNA levels of sst5, sst5TMD4 and sst5TMD5 variants and the SSTR5-AS1 by qPCR in a cohort of 11 normal pituitary (NPs) and 27 somatotropinoma samples. In addition, we studied the methylation status in four CpG areas of *SSTR5* and *SSTR5-AS1* genes. Our results revealed that somatotropinomas expressed significantly more sst5 than NPs, whereas no significant differences were found in the expression of the antisense transcript. In addition, expression of sst5TMD4 and sst5TMD5 variants was numerically, although not significantly increased in this pilot cohort of patients. Methylation analysis revealed that CpG sites were differentially methylated on *SSTR5* and *SSTR5-AS1* genes in acromegaly compared with NPs, which might explain the differential expression of sst5. Interestingly, mRNA levels of *SSTR5* showed a direct correlation with *SSTR5-AS1* expression, but not with those of the sst5 splicing variants, both in acromegaly and NP samples, which could suggest that the antisense may regulate the expression of the full-length *sst5*, without affecting its splicing variants. Summarizing, results from this work supports the notion that epigenetic and post-transcriptional events might contribute to regulate the expression of *SSTR5* in acromegaly, while their precise involvement in *SSTR5* splicing dysregulation remain to be determined.

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Pituitary Clinical

GP202

Endoscopic vs microscopic transsphenoidal surgery for Cushing's disease: a systematic review and meta-analysis

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Background
Cushing's disease is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma, resulting in glucocorticoid excess. First-choice treatment is transsphenoidal pituitary surgery, using either a microscopic or endoscopic technique. Convincing evidence supporting the choice for one of both techniques, either based on treatment results or complication rate, is lacking.
Objective
We aimed to compare endoscopic and microscopic transsphenoidal surgery for Cushing's disease regarding surgical outcomes (remission, recurrence, and mortality) and complication rates, and to stratify the results by tumor size.
Methods
Nine electronic databases were searched in February 2017 to identify potentially relevant articles. Cohort studies assessing surgical outcomes or complication rates after endoscopic or microscopic transsphenoidal surgery for Cushing's disease were eligible. Pooled proportions were reported including 95% confidence intervals.
Results
We included 97 articles with a total of 6695 patients (5711 microscopically and 984 endoscopically operated). Overall, remission was achieved in 5177 patients (80%), with no clear difference between the two techniques. Recurrence was around 10% and short term mortality $<0.5\%$ for both techniques. Cerebrospinal fluid leak occurred more often in endoscopic surgery (12.9% vs 4.0%), whereas transient diabetes insipidus occurred less often (10.4% vs 18.5%). For microadenomas, results were comparable between both techniques. For macroadenomas, the percentage of patients in remission was higher after endoscopic surgery (76.3% vs 59.9%), and the percentage recurrence was lower after endoscopic surgery (1.5% vs 17.0%).
Conclusion
This meta-analysis shows that for patients with Cushing's disease endoscopic surgery reaches comparable results for microadenomas, and probably better results for macroadenomas than microscopic surgery. These results are obvious despite the presumed learning curve of the newer endoscopic technique, although confounding cannot be excluded. Based on this study, the endoscopic technique may be considered the current standard of care, microscopic neurosurgical pituitary centers should at least consider referring Cushing's disease patients with a macroadenoma.

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GP203

Factors predicting comorbidities in cured patients with Cushing's syndrome

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Introduction
In patients with cured Cushing's syndrome, comorbidities often persist after remission of glucocorticoid excess. Here we investigate long-term comorbidities in patients with Cushing's syndrome in remission, and their relationship to metabolic and hormonal markers at the initial diagnosis of the disease.
Methods/design
We evaluated 118 patients with cured Cushing's syndrome (55 Cushing's disease, 55 adrenal Cushing's syndrome and 8 ectopic Cushing's syndrome) 10 years (range 2–29) after the last surgery. Anthropometric, metabolic, hormonal parameters and comorbidities (obesity, diabetes, hyperlipidaemia, hypertension, osteoporosis, depression) at the last follow-up visit were obtained; baseline data on parameters at diagnosis of Cushing's syndrome were extracted from hospital records. Uni- and multivariate regression analysis was performed for testing the relationship between baseline factors and long-term comorbidities.
Results
Inpatients with manifest comorbidities at diagnosis, Cushing's remission resolved diabetes in 54% of cases, hypertension in 34% of cases, hyperlipidaemia in 28% and depression in 48% of cases. Ten (range 2-29) years after the last surgery the prevalences of comorbidities in cured patients were: obesity 16%, diabetes 12%, hypertension 58%, hyperlipidaemia 62%, depression 16% and osteoporosis 21%. In a multivariate regression analysis, age, fasting glucose and depression at Cushing's diagnosis, were positive predictors of the number of long-term comorbidities, while baseline urinary free cortisol secretion negatively correlated with the persistence of comorbidities in the long-term. The negative relationship between baseline 24-h urinary cortisol secretion and long-term comorbidities was also found when pituitary and adrenal Cushing's cases were analysed separately.
Conclusions
Long-term comorbidities after remission of Cushing's syndrome depend not only on the presence of classical cardiovascular risk factors such as age and hyperglycaemia at diagnosis, but also on the amount of glucocorticoid excess. Lower baseline urinary cortisol levels are associated with more long-term comorbidities, possibly due to the delayed diagnosis in milder Cushing's syndrome leading to a longer exposure to excess glucocorticoids.

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GP204

Long-term efficacy and safety of once-monthly pasireotide in patients with Cushing's disease: A Phase III extension study

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Introduction
The 12-month results of a multicentre, double-blind, Phase III study showing the efficacy and safety of a monthly, long-acting formulation of pasireotide in Cushing's disease (CD) patients have been reported previously (Lacroix *et al. Lancet Diabetes Endocrinol* 2018). The results of the extension phase of this study are reported here.
Methods
Patients ($n=150$) with persistent/recurrent or *de novo* CD and mean urinary free cortisol (mUFC) 1.5–5× the upper limit of normal (ULN) were randomized to monthly pasireotide 10mg ($n=74$) or 30 mg ($n=76$). Up-titration was permitted at month (M) 4, M7, M9, or M12. Patients could enter an optional, open-ended extension if they had mUFC≤ULN at M12 and/or experienced significant clinical benefit in the investigator's opinion. Investigators and patients were unblinded after the M12 analyses were completed. Data from both dose groups were pooled for this analysis.
Results
Of 104 patients who completed the core study, 81 entered the extension. Median (range) exposure for patients who entered the extension was 23.9 (12.0–55.3) months. Of patients who entered the extension and had a valid mUFC assessment at the given time point, a controlled response (mUFC≤ULN) occurred in 42/81 (51.9%; 95%CI: 40.5,63.1) patients at M12, 38/58 (65.5%; 95%CI: 51.9,77.5) patients at M24, and 13/18 (72.2%; 95%CI: 46.5,90.3) patients at M36. Median (range) change from baseline in mUFC was −51.9% (−98.7,422.3) at M12, −64.1% (−97.8,356.0) at M24, and −68.3% (−99.2,−12.7) at M36. A ≥20% tumour-volume reduction from baseline was seen in 25/38 (65.8%) patients at M24 and 9/14 (64.3%) patients at M36; 10/14 (71.4%) and 4/4 (100%) patients with a pituitary macroadenoma (maximum diameter ≥10 mm) at baseline had a ≥20% reduction at M24 and M36, respectively. Improvements in clinical signs, including systolic/diastolic blood pressure and weight, were seen at M24 and M36. The safety profile of pasireotide was consistent with previous experience, with no new safety signals detected during the extension. Median (range) change from baseline in HbA_{1c} was 0.9% (0.8,1.2) at M24 and 0.8% (−0.2,2.2) at M36. After the M12 data cut-off, grade 3 adverse events (hyperglycaemia, hypertension, hypoglycaemia) were reported in three more patients; no grade 4 adverse events were reported.
Conclusion
Long-term treatment with long-acting pasireotide provided sustained biochemical and clinical improvements and reduced tumour volume, with no new safety signals emerging. These data support the use of long-acting pasireotide as an effective long-term treatment for some patients with CD.

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GP205

Predictors of response to long-acting pasireotide in patients with Cushing's disease during a Phase III study

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Introduction
Long-acting pasireotide reduced urinary free cortisol (UFC) in most patients with Cushing's disease (CD) during a large Phase III study (Lacroix *et al. Lancet Diabetes Endocrinol* 2018). The analyses presented here explored the impact of baseline characteristics on response to long-acting pasireotide.
Methods
150 patients with persistent, recurrent or *de novo* CD and mean UFC (mUFC; from three 24-hour samples collected over 2 weeks) of 1.5–5xULN were randomized to monthly pasireotide 10 mg/30 mg. Dose up-titration was permitted at month (M) 4, M7, M9, and/or M12. Primary endpoint: mUFC≤ULN at M7. As response rates were similar between dose groups, data were pooled for the current analyses.
Results
41.3% ($n=62/150$) of patients achieved mUFC≤ULN at M7 (responders). Of patients with mUFC≤ULN at M3, 73.3% ($n=33/45$) were responders at M7, compared with 27.6% ($n=29/105$) of those with mUFC>ULN at M3. Baseline mean [S.D.] mUFC was numerically lower in responders than in non-responders (424.1 [308.8] vs 502.3 [284.1] nmol/24 h; $P=0.11$). Other baseline mean (S.D.) values in responders and non-responders were, respectively: serum cortisol, 571.3 (184.5) and 575.1 (207.5) pmol/l; late-night salivary cortisol, 12.2 (13.7) and 9.3 (6.6) nmol/l; maximum tumour diameter, 9.9 (4.5) and 9.8 (6.8) mm. Higher response rates were seen in patients with lower baseline mUFC; response rates were similar in other subgroups analysed (Table).
Response rate by baseline characteristic
Conclusion
Lower baseline mUFC and early control of mUFC after initiation of long-acting pasireotide were associated with higher response rates at M7.

Table 1

	n	**Response rate, %** (95%CI)
Surgical status		
No prior surgery	27	40.7 (22.4–61.2)
Prior surgery	123	41.5 (32.7–50.7)
Sex		
Male	32	40.6 (23.7–59.4)
Female	118	41.5 (32.5–51.0)
Age quartile (range, years)		
Q1 (18–27)	31	32.3 (16.7–51.4)
Q2 (28–36)	42	40.5 (25.6–56.7)
Q3 (37–46)	38	50.0 (33.4–66.6)
Q4 (48–71)	39	41.0 (25.6–57.9)
mUFC quartile (range, nmol/24 h)		
Q1 (44.7–272.5)	37	54.1 (36.9–70.5)
Q2 (277.6–392.5)	38	47.4 (31.0–64.2)
Q3 (400.8–603.9)	37	32.4 (18.0–49.8)
Q4 (607.3–1670.0)	38	31.6 (17.5–48.7)
Adenoma size*		
Microadenoma	68	35.3 (24.1–47.8)
Macroadenoma	49	49.0 (34.4–63.7)
Non-visible	29	44.8 (26.4–64.3)
Maximum tumour diameter quartile (range, mm)		
Q1 (3–5)	22	36.4 (17.2–59.3)
Q2 (6–8)	35	42.9 (26.3–60.6)
Q3 (9–11)	27	29.6 (13.8–50.2)
Q4 (12–54)	33	51.5 (33.5–69.2)

*By maximum diameter (microadenoma>0–<10 mm; macroadenoma≥10 mm)

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GP206

Clinicopathological correlations in pituitary thyrotroph tumors from a cohort of 23 patients

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The thyrotroph tumors or pituitary neuroendocrine tumors (PitNET) classify as tumors of Pit-1 family. These tumors are rare and may be monohormonal, secreting only TSH, or plurihormonal, secreting TSH-GH ± PRL, with or without acromegaly. The objectives of this retrospective study were to confirm the frequency of the plurihormonal subtype and to compare the clinical, biological and pathological characteristics of these two pathological subtypes. We retrospectively studied the medical records of 23 patients with thyrotroph tumors treated by transphenoidal surgery. Routine staining and immunohistochemistry with the following antibodies against the hormones (PRL, GH, ACTH, βFSH, βLH, βTSH, and α-subunit), the somatostatin receptors ($SSTR_{2A}$, $SSTR_5$), and the transcription factor Pit-1 were performed. The proliferative rate (mitoses and Ki-67 index) and the p53 expression were also studied. The pituitary tumors were classified taking into account the invasion and the proliferation. All the tumors, except one with clinical and biological hyperthyroidism, expressed TSH. Half were monohormonal ($n=11$) and out of the 12 plurihomornal ones, 6 were positive for both TSH and GH. Two tumors expressed TSH, PRL and GH and 4 were positive for TSH and PRL. Only 3 patients with GH co-expression presented clinical and biological signs of acromegaly. Three TSH monohormonal tumors are silent. The symptoms of hyperthyroidism and goiter were more frequent in the plurihormonal tumors than in the monohormonal ones probably due to GH effect on thyroid facilitating the goitre occurrence. Almost all the thyrotroph tumors expressed Pit-1 and $SSTR_{2A}$ with a high score (>5). Monohormonal and plurihormonal TSH-PRL tumors were characterized by polymorphous cells, a high expression of $SSTR_{2A}$, but no or low expression of $SSTR_5$. The plurihormonal TSH-GH ± PRL subtype ($n=8$) had a higher expression of both $SSTR_{2A}$ and $SSTR_5$ and 4 of them exhibited cytological features of the somatotroph type. Fibrosis and calcifications were frequent in both tumor types. We did not observe differences regarding the proliferative rates and the grading of the tumors. In conclusion, this study confirms that these tumors, belonging to the Pit-1 family, are frequently plurihormonal, secreting mainly TSH-GH, and express SSTRs. The first line therapy is the transsphenoidal surgery, but complementary treatment by somatostatin analogues may be proposed, according to the expression of SSTRs by the tumor.

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GP207

Molecular profiling of non-functioning pituitary adenomas does not support pharmacological therapeutic options

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Non-functioning pituitary adenomas (NFPA) are the most common pituitary tumours. They usually come to medical attention because of a mass effect and/or hypopituitarism. Tumour shrinkage during therapy with either dopamine agonists (DA) or somatostatin analogues (SSA) has been previously reported in some cases; however, response of NFPA to medical treatment is still poor and unpredictable. Our aim was to explore the molecular mechanisms underlying this lack of efficacy through evaluation of genes involved in therapeutic response to SSA and DA. Expression of 13 genes was analyzed in 105 acromegaly samples (ACRO), 20 NFA and 14 control pituitaries (CP) from autopsies and organ donors. The genes (*SSTR2*, *SSTR5*, *DRD2* long and short isoforms, *AIP, CDH1, Ki67, ARRB1, GHRL, IN1-GHRL, KLK10*, *PLAGL1* and *PEBP1*) were measured by RT-qPCR using TaqMan technology and the levels were normalized by three reference genes (*MRPL19*, *TBP* and *PGK1*).

Results

DDR2, SSTR2 and *SSTR5* showed significantly and absolute lower expression levels in NFA compared to ACRO ($P<0.01$ for all comparisons) and CP ($P<0.01$ for all comparisons). Moreover, *SSTR5* levels were extremely low in NFPA, pointing to a potential absolute negative therapeutic response to the second generation SSA Pasireotide compared to first generation SSA. Unsupervised clustering showed that NFPA were extremely different from CP and ACRO tumours according to the expression of these markers. Tumour size in NFPA significantly correlated with *AIP* and *IN1-GHRL* (Pearson's $r=0.48$ and $P=0.03$, Pearson's $=0.47$ and $P=0.04$, respectively); and showed a trend to correlation with *ARRB1* and *PLAGL1* levels (Pearson's $r=0.42$ and $P=0.07$, Pearson's $=-0.45$ and $P=0.05$, respectively). Moreover, *ARRB1* was significantly overexpressed in tumours that did not achieve complete remission after surgery (fold change $=1.81$, $P=0.01$). In addition, *RKIP* and *KLK10* showed a positive correlation trend with extrasellar extension (fold change $=1.39$ and $P=0.07$, fold change $=3.74$ and $P=0.07$, respectively). These preliminary results suggest that some molecular markers may identify NFPA with a higher potential for growth and invasiveness, thus contributing to therapeutic decisions regarding reoperation or radiotherapy but do not support the use of targeted drug according to the studied molecular profiling.

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GP208

The role of clomiphene citrate in the resolution of hypogonadism in male patients with prolactinomas under cabergoline therapy

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Background

Dopamine agonists (DA) are the treatment of choice of prolactinomas. Cabergoline is preferable to bromocriptine due to its greater effectiveness and better tolerabilitiy. However, up to 30–50% of male patients may persist with low levels of testosterone despite prolactin (PRL) normalization under DA therapy or the use of the maximum tolerated dose of DA. The aim of this prospective open study was to evaluate the efficacy of the SERM clomiphene citrate (CC) in these cases.

Subjects and methods

The aim of this prospective study was to evaluate the efficacy of CC in normalizing total testosterone (TT) in prolactinomas patients with persistent hypogonadotropic hypogonadism (HH) despite the use of CAB in weekly doses of up to 3 mg/week. TT, estradiol (E2), LH, FSH, and PRL were measured before and 4, 8, and 12 weeks after CC. Erectile function and hypogonadism symptoms were evaluated before and after CC. Persistent HH was defined by TT levels <300 ng/dl, along with either normal/low LH and FSH levels after at least 6 months of DA therapy. Response to CC was defined as TT levels ≥ 300 ng/dl.

Results

Eighteen patients (72%), 10 hyperprolactinemic and 8 normoprolactinemic, responded to clomiphene (TT ≥ 300 ng/dl). Their mean TT levels were 234.1 ± 36.6 ng/dl before CC and 390.1 ± 38.9 ng/dl 12 weeks later ($P<0.01$). Significant increases were also observed in FSH and LH concentrations ($P<0.01$). PRL levels remained unchanged and E2 did not significantly differ when baseline and 12 weeks levels were compared. Erectile function improved in all responsive patients.

Conclusion

Clomiphene restored normal testosterone levels in most male patients with prolactinomas and persistent hypogonadism under CAB therapy. Recovery of gonadal function by clomiphene was independent of PRL levels.

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GP209

Cabergoline - therapy for 121 giant invasive prolactinomas

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Objective
Prospective study of cabergoline effect in newly diagnosed patients with giant invasive prolactinomas.
Patients and methods
The study group included 121 patients with giant prolactinomas (tumors larger than 40 mm in size); among them 49 patients had tumors larger than 60 mm in size. 91 male and 30 female aged 16–67 years (median 37) were treated with 0.5–3.5 mg/week (mean 1.5 mg) cabergoline. The treatment period was 6–120 months (median 18).
Results
Before treatment 117 (97%) patients had hypogonadism, 99 (82%) - visual impairments, 71 (59%) - headaches, 29 (24%) - epileptic syndrome. Serum prolactin level before treatment ranged between 12990 and 2210000 mU/l (median 198000; normal 30–545 mU/l). Decrease of prolactin occurred in 114 (94%) patients; prolactin level was normalized during treatment in 49% of cases; 98/121 (81%) patients had significant adenoma shrinkage; 77/99 (78%) patients with pre-treatment visual abnormalities had visual improvement, 67/71 (95%) - headache regression. In 17 patients cerebrospinal fluid (CSF) leakage occurred within 3–6 weeks, in 1 case - in 76 months after initiation of treatment. In 15 patients endoscopic endonasal surgery for fistula repair was performed; in two patients the CSF leakage ceased after diuretic therapy and temporarily cabergoline dosage decrease; 7 (6%) patients had rapid progression cabergoline-resistant tumors. They had surgery followed by stereotactic radiotherapy. PRL-secreting pituitary carcinomas with intra- and extracranial metastases were diagnosed in three cases; 5 (4%) patients showed tumor enlargement due to intratumoral hemorrhage.
Conclusion
Cabergoline should be the first-line therapy for giant invasive prolactinomas. Use of cabergoline results in effective reduction of prolactin, improvement of visual defects and provides tumor shrinkage. However, patients with giant prolactinomas are at a risk of CSF leakage and tumor enlargement during primary cabergoline treatment.

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GP210

Endocrine disorders in adults after allogenic hematopoietic stem cell transplant

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Background
Over the last 20 years there have been significant advances in stem cell transplantation (SCT) in adults for haematological malignancies leading to improved survival. Endocrine disorders are among the most common complications in survivors after hematopoietic allogeneic stem cell transplant (HSCT), but data on adult transplant patients are still scarce.
Methods
This is a retrospective study which included 284 adult patients (94 females and 190 males) who underwent allogeneic HSCT between 2002 and 2014 in a University Irish Hospital. All patients were preconditioned with chemotherapy and total body irradiation (TBI). One hundred and thirty four patients received allogeneic HSCT from unrelated donors. The functions of the hypothalamic-pituitary-gonadal/thyroid/adrenal/somatotroph axis were evaluated at time of last review.
Results
The mean age of the patients at diagnosis was 33.3 (s.d. $\pm$10.6) years old with a mean age at transplant of 35.2 (s.d. $\pm$10.3) years old. 11.3% of the patients tested ($n=44$) had low morning cortisol levels at 16 months post-transplant and 25% of the patients tested ($n=12$) had hyperprolactinemia at 6 months post-transplant. Insulin-like growth factor-1 was tested in only 13 patients with below the normal range value in one patient (7.6%) and above normal range values in 2 patients (15.2%). Beyond one-year post - transplant, 39% of the patients had abnormal thyroid function tests of which 15% ($n=10$) displayed biochemical features of central hypothyroidism. Out of 54 women tested, 8 (14.8%) displayed biochemical features of hypogonadotropic hypogonadism and 33 (61.1%) had hypergonadotropic hypogonadism. In males, out of 108 tested, 2 (1.8%) had hypogonadotropic hypogonadism and 67 (62%) had hypergonadotropic hypogonadism. Out of 104 patients tested, 21.1%had a raised sex hormone binding globulin (SHBG). Men were more likely than women to develop hypergonadotropic hypogonadism ($P<0.01$). Patients with normal LH and FSH were more likely to be older compared to patients with a raised LH and FSH (35.9 Vs 31.5 years old, $P<0.01$). SHBG was more likely to be raised in patients with raised LH and FSH ($P<0.01$). Oestradiol levels but not testosterone levels were more likely to be influenced by age ($P=0.01$ vs $P=0.1$).
Conclusion
These data suggest that adults undergoing HSCT are at a high risk of endocrine dysfunction. These patients require early endocrinology input and long-term surveillance for the detection and treatment of endocrine disorders.

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GP211

A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors

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Background
Monoclonal antibodies targeting CTLA-4 and PD-1/PD-L1 are promising for a wide range of advanced malignacies. These immune checkpoint inhibitors (ICI) provoke endocrine adverse events including hypopituitarism and primary thyroid disease.
Methods
PubMed was searched through August 22nd, 2017, for relevant articles on endocrinopathies and ICI, by two reviewers independently (J.d.F. and C.A.). The weighted incidence and odds-ratio were estimated for hypophysitis, primary thyroid disease, primary adrenal insufficiency and diabetes mellitus. Their management is discussed in a systematic review.
Results
One hundred and one clinical studies (retrospective, prospective and randomized trials) involving 19.922 patients were included. Patients treated with ipilimumab experienced hypophysitis in 5.6% (95% CI, 3.9–8.1) which was higher than PD-1 treated patients (nivolumab, 0.5%; 95% CI, 0.2–1.2; pembrolizumab, 1.1%; 95% CI, 0.5–2.6). Tremelimumab (anti-CTLA-4) was also less likely to induce hypophysitis (1.8%; 95% CI, 1.1–2.9). Patients on PD-1/PD-L1 inhibitors had a higher incidence of primary thyroid dysfunction – particularly hypothyroidism (nivolumab, 8.0%; 95% CI, 6.4–9.8; pembrolizumab, 8.7%; 95% CI, 7.9–9.6; PD-L1, 5.5%; 95% CI, 4.4–6.8; versus ipilimumab, 3.8%; 95% CI, 2.6–5.5). Combination therapy was associated with a higher incidence for both hypothyroidism (10.2–16.4%) and hypophysitis (8.7–10.5%). Diabetes mellitus and primary adrenal insufficiency, rare findings on monotherapy, were substantially more frequent on combined therapy.
Conclusion
Our systematic review and meta-analysis demonstrates a high incidence of endocrine adverse events provoked by single agent checkpoint blockade which is further reinforced by combined treatment.

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GP212

Predictors of failure to respond to fluid restriction and furosemide efficacy prediction in patients presenting Syndrome of Inappropriate Antidiuretic while receiving parenteral nutrition. Prospective Multicenter Study

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Introduction
Syndrome of Inappropriate Antidiuretic (SIAD) is the most frequent cause of hyponatremia in parenteral nutrition (PN) patients. Yet studies concerning SIAD therapy are lacking. Our objective was to describe SIAD treatment and determine pre-treatment predictors of failure to respond to fluid restriction (FR) and furosemide efficacy prediction in a group of patients with SIAD while receiving PN.
Methods
Prospective, non-interventional, multicenter study in 19 Spanish hospitals. Forty-seven patients with SIAD-induced hyponatremia while receiving PN were recruited. Hyponatraemia was defined as a Serum Na level (SNa) <135 mmol/l. A positive response to therapy was defined as reaching SNa >135 mmol/l (eunatremia) following 72 hours of treatment. Urine osmolality-UOsm- $>$ 500 mOsm/kg, a Furst formula (ratio Urine Sodium + Urine Potassium/SNa) >1, or a 24-hour urine volume <1500 ml were all considered predictors of a negative response to FR. A UOsm >350 mOsm/kg was considered a predictor of a positive response to furosemide. The therapy used for the treatment of hyponatremia in these patients was also collected.
Results
59.6% were men. The average age was 66.9 (S.D. 11,5). All patients had diagnostic criteria for the diagnosis of SIAD. 20/47 received treatment: (80% FR, 10% FR and furosemide, 10% tolvaptan). No patient achieved FR to $\leq$ 1 liter/24 h. 26/47 (55.3%) patients had UOsm >500 mOsm/kg, 16/44 (36.4%) had a Furst formula>1 and 8/36 (22.2%) had a urinary volume <1500 ml/24 h. Thus, 68.1% had at least one criterion predicting a lack of response to FR. 69.6% had UOsm >350 mOsm/kg, and would be candidates for furosemide therapy. The percentage of patients achieving eunatraemia following 72 hours was: 40% with FR, 100% with furosemide, 100% with tolvaptan.
Conclusions
In parenteral nutrition patients with SIAD, fluid restriction is by definition difficult to achieve, and could compromise nutritional treatment. Furthermore, it is ineffective, with more than two-thirds of patients presenting predictors of non-response. Yet fluid restriction was the therapy most frequently used to treat SIAD-induced hyponatremia in this series of patients. Furosemide and tolvaptan should be considered first-line therapy for the treatment of SIAD in patients receiving parenteral nutrition.

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GP213

Abstract withdrawn.

Reproduction

GP214

Sperm DNA fragmentation index as a promising predictive tool for male infertility diagnosis and treatment management

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Background
Conventional parameters evaluated in semen analysis show several limits in the diagnostic setting of male infertility and do not provide any useful prognostic tool for assisted reproductive technique (ART). On the contrary, the assessment of sperm DNA fragmentation (sDF) was proposed to discriminate fertile from infertile men and to predict the follicle stimulating hormone (FSH) treatment response in infertile men. However, a comprehensive evaluation thereof is not available so far.
Purpose
This meta-analysis was designed to assess the sDF power in the diagnosis of male infertility and, in addition, to assess the sDF role in predicting FSH therapy response in infertile men.
Methods
Two literature searches were conducted. Firstly, both interventional and observational clinical trials comparing fertile to infertile/subfertile men were included. Secondly, interventional/observational clinical trials evaluating FSH-treated infertile men were assessed.
Results
Twenty-eight studies were included in the first analysis. sDF levels resulted significantly higher in infertile men ($P<0.001$), independently from the sDF method applied. ROC curves identified a sDF threshold of 20%, with a sensitivity of 79% and a specificity of 86%. Six studies were included in the second analysis, showing a significant sDF improvement ($P=0.04$) of 4.24% (C.I.: 0.23–826%) after 3 months of therapy. This sDF improvement was in line with the sperm number improvement ($P<0.001$), suggesting a similar efficacy in this setting.
Conclusion
This meta-analysis demonstrates the sDF relevance in male infertility assessment, showing a higher accuracy in detecting sperm function than conventional semen parameters. Although larger and properly designed prospective trials are needed before sDF may be adopted as an established diagnostic and prognostic test in male infertility, for the time it represents the most promising tool in clinical and research practice.

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GP215

Alleviation of perfluorooctanesulfonate (PFOS)-induced disruption of blood-testis barrier by altering cell signaling molecule expression in human sertoli cells.

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Perfluorooctanesulfonate (PFOS) and its related product perfluorooctanic acid (PFOA) are anthropogenic fluorosurfactants widely used in consumer products. In general, studies in rodents have supported the conception that PFOS perturbs testis function, such as by inducing Sertoli cell injury. It remains to be demonstrated if similar effects could be reproduced in humans. We sought to examine its effects on human spermatogenesis by using a human Sertoli cell primary culture system. Human Sertoli cells were cultured in chemically defined medium in the presence of 10% fetal bovine serum so that these cells remained mitotically active and could be re-used after multiple passes. They were used for *in vitro* cell junction formation studies and for the overexpression of cDNA constructs to identify the molecular mechanism that mediated toxicant- induced Sertoli cell injury. We also sought to examine possible FAK-mediated rescue function which could protect human Sertoli cell against PFOS-induced cell injury. Transfection of the human Sertoli cells for overexpression of target genes such as FAK and its mutants were performed. PFOS was found to induce human Sertoli cell injury through its disruptive effects on the actin microfilaments and microtubule (MT) organization across the Sertoli cell cytosol, making these cytokeletons failed to support cell adhesion at the Sertoli cell-cell interface that constituted the blood-testis barrier. However, an overexpression of a FAK phosphomimetic mutant p-FAK-Y407E (constitutively active) by converting amino acid residue Tyr-407 to Glu-407 was able to rescue the PFOS-induced Sertoli cell injury through proper organization of actin microfilaments and MTs across the Sertoli cell cytosol. Alternatively, since we have shown that the Sertoli cell BTB function is mediated by mTORC1 complex through rpS6, involving Akt1/2 (a family of serine/threonine kinase) downstream in a more recent study in rodents, overexpression of a constitutive active phosphor-mimetic mutant of p-Akt1-T308 (such as p-Akt1-T308E, by mutating Thr(T)-308 to Glu(E)-308) was also conducted. In short, PFOS is a toxicant which could induce Sertoli cell injury in humans, similar to its toxic effects in rodents. The PFOS-induced Sertoli cell adhesion function through changes in the organization of actin and MT

cytoskeletons could be rescued by overexpression of phosphorylated signaling molecules.

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GP216

Sertoli cell-specific knockout of coxsackie and adenovirus receptor (Cxadr) disrupts the blood-testis barrier and causes impaired fertility

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Coxsackievirus and adenovirus receptor (CXADR) is localized at the blood-testis barrier (BTB) and at the interface between Sertoli cells (SC) and germ cells (GC). Earlier studies indicated that CXADR plays role in BTB function and germ cell migration. However, conventional knockout of CXADR leads to embryonic lethality, making the study of CXADR in the testis impossible. We aim to generate SC-specific CXADR knockout (KO) mice to evaluate the SC-specific function of CXADR on spermatogenesis in vivo. RNA sequencing and bioinformatics analyses were employed to identify and unravel the regulatory mechanisms that may involve in reproductive impairment. The SC-specific deletion of CXADR under the control of *Amh* promoter was confirmed by PCR and immunohistochemistry. Adult SC-$Cxadr^{-/-}$ mice exhibited significant reductions in fertility efficacy (>40% reduction) and testes/body weight ratio due to GC loss. Compromised BTB function coupled with down-regulation or mislocalization of the BTB components including occludin/ZO-1 complex and β-catenin have been observed in SC-$Cxadr^{-/-}$ testes. Transcriptomic and proteomic analyses of SC-$Cxadr^{-/-}$ testes revealed that the enriched gene ontology (GO) terms are highly related to male reproduction. Rap1/Wnt/Hippo signaling network and its core mediators such as β-catenin and Cdc42 were predicted in pertinent to fertility impairment in SC-$Cxadr^{-/-}$ testes via genome-wide data analyses. Besides, Wnt/Hippo targets including *Wnt5a*, *Wnt6*, *Wnt9a, Myc* and *Snai2* were also significantly altered in SC-$Cxadr^{-/-}$ testes. Activation of β-catenin and inhibition of Cdc42 with disorganized F-actin at the apical ES were observed in SC-$Cxadr^{-/-}$ testis and cultured $Cxadr^{-/-}$ SCs ($Cxadr^{-/-}$ MSC-1 cells). Overexpression of constitutively active Cdc42 in $Cxadr^{-/-}$ MSC-1 cells could partially recover the CXADR-mediated inhibition of non-phosphorylated β-catenin and F-actin filaments. Apparently, apart from being a structural protein at the BTB, CXADR functions as a crucial signaling mediator to trigger the downstream effects on junction disruption and actin reorganization via non-phosphorylation of β-catenin and Cdc42 inhibition. Taken together, CXADR in SCs affects the BTB function and F-actin organization via crosstalk of CXADR/β-catenin/Cdc42. SC-CXADR plays an indispensable role in spermatogenesis.

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GP217

The first Belgian series of 56 patients with congenital hypogonadotropic hypogonadism (CHH): genetic and brain abnormalities

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Introduction
CHH is a genetic syndrome that combines reproductive and brain abnormalities. The brain phenotype has been incompletely characterized. We aimed to study neuroradiological and genetic features in this first Belgian series of patients with CHH.

Methods
A series of 56 adult patients (48 males, 8 females) presenting with CHH was investigated for a panel of 16 genes related to hypogonadotropic hypogonadism by next generation sequencing on a MiSeq® Instrument (Illumina) and by using a validated targeted approach with xGen® Lockdown® Probes (IDT). We then reviewed cerebral or hypothalamic-pituitary abnormalities in 32 patients using magnetic resonance imaging (MRI).
Results
Among the 56 patients, we found, up to now, some 26 genetic variants including FGFR1, GnRHR, CDH7, TAC3, WDR11, HS6ST1, PROKR2 and KISSR genes. In this series, five new variants (class3 to 5) were present in the following genes: TAC3 gene (c.238+1 G>A, class 5), FGFR1 gene (c.169C>A, p.Leu57Met, class 3), CDH7 gene (c.7212_7214del,p.Arg2405del, class 3), KISS1R (c.502G>A, p.Val168Ile, class 3) and a deletion of KISSR. A total of 21 patients presented a normal brain MRI, whereas 11 other patients presented structural abnormalities: a Chiari type 1 malformation (CM1) ($n=3$), an anterior pituitary hypoplasia ($n=3$), a Rathke's pouch cyst ($n=1$), a septo-optic dysplasia ($n=2$), an hydrocephalus ($n=1$) and an aracnoidal cyst ($n=1$). Among the group of abnormal MRI, only one patient with CM1 presented a new pathogenic variant in *FGFR1* gene (c.1025T>A; pLeu342*). Among the 21 patients with normal MRI, seven patients were heterozygous for one pathogenic variant.
Discussion
In our cohort, CM1 was found in three of the 32 patients (9.3%) who performed a brain MRI. In the general population, incidence of CM1 is estimated at 0,7%. CM1 and CHH have not been previously reported, although CM1 and cerebellar herniation were seen in GHD or in multiple hormone deficiency patients. We found a new *FGFR1* mutation for one of our patients with CM1. Common variants in genes involved in somitogenesis and fetal vascular development may confer a susceptibility for CM1: the contribution of FGFR1 to these defects deserve more investigations.
Conclusion
In this large Belgian series of CHH patients, we describe, for the first time, five new pathogenic variants. Moreover, we suggest a new syndromic association between CHH and CM1. Multicenter studies and systematic brain MRI may be required to extend the phenotype and the genotype of CHH patients.

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GP218

Bioassay-based characterization of novel androgens

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Chemical-analytical methods are currently in use as the gold standard approach for the detection of androgens, designer androgens and selective androgen receptor modulators (SARMs) in serum and urine samples from athletes as well as in sports supplements. These methods are exquisitely sensitive and selective. However, they have the disadvantage in that the androgens that being surveyed for must have delineated structures. Designer androgens or SARMs that have divergent structures from the characterized reference list can be missed with analyte methods because their specific analytical fingerprints are not defined. In vitro cell based androgen receptor (AR) bioassays are based on probing the biological pathway of androgen action and therefore are capable of identifying the presence of any AR-activating compound in a sample. Moreover, by basing the AR bioassays in different host cells (eg. yeast- no metabolism or cofactors; HEK293- limited metabolism but has cofactors; HuH7- active metabolism and cofactors) the relative AR potency of activating compounds can be measured. Using this tandem AR bioassay approach, 15 SARMs, recently detected as sports doping agents, were analyzed for relative AR potency. For S-1, S-6, S-23, S-24, ostarine, andarine, LG-121071, Rad-140, LGD-2226, 93746 and BMS-564929 all showed only moderate intrinsic AR bioactivity in the yeast bioassay, however potency increased dramatically with active metabolism. Some of these SARMs showed AR potencies far beyond that measured for the endogenous androgens, testosterone or dihydrotestosterone. AC262536 and MK0773 were weak SARMs even after active metabolism. By contrast, ACP-105 and YK-11 were both potent SARMs, with and without metabolism. Together, these results have implications for the anabolic potential of these SARMs, thus they pose a real threat to sports doping.

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GP219

Mitochondrial phenotype of FOXL2 variants associated with Blepharophimosis, Ptosis and Epicantus Inversus Syndrome (BPES)

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Primary ovarian insufficiency (POI) is a highly heterogeneous condition defined by the occurrence of amenorrhoea, hypoestrogenism and hypergonadotropinism in women under 40. POI onset can be triggered by multiple factors, such as iatrogenic events, environmental conditions, autoimmunity or genetic alterations. When the ovarian insufficiency occurs as a consequence of either chromosomal or genetic alterations, it can be associated with other congenital abnormalities and classified as part of a syndrome. Genetic alterations of the transcription factor FOXL2 are associated with the onset of the blepharophimosis, ptosis and epicantus inversus syndrome (BPES), an autosomal dominantly inherited condition in which eyelid dysplasia occur either in association (BPES type 1) or not (BPES type 2) with POI. By genetic screening of several BPES-affected women we identified two novel nonsense FOXL2 variants: p.E92* variant in a fertile woman with regular menses at the time of sampling and her prepuberal daughter, and p.Y186* variant in a woman with primary amenorrhea. To unravel the impact of the novel variants on protein function, the subcellular localization of WT and mutant FOXL2 was investigated in transiently transfected HeLa cells by confocal microscopy. Surprisingly, while both FOXL2-WT and FOXL2-p.Y186* signals were confined to the nucleus, mislocalization of the FOXL2-p.E92* variant to mitochondria was revealed by colocalization with the mitochondrial marker TOM20 and confirmed by cellular fractionation. Moreover, evaluation of mitochondrial morphology in FOXL2-p.E92* cells revealed a significant shift from an interconnected network of mitochondria to a more fragmented state compared to FOXL2-WT- and FOXL2-p.Y186* cells. On this regard, it is widely known that mitochondrial fusion-to-fission rate is finely tuned in response to metabolic or environmental stress, and that an increase in mitochondrial fission enables the removal of damaged mitochondria and facilitates apoptosis. The increase in mitochondrial fragmentation in FOXL2-p.E92* cells therefore suggests that this variant might have a toxic effect on cell metabolism. This hypothesis is further supported by its increased degradation by the ubiquitin-proteasome system, as confirmed by treatment with the proteasome inhibitor MG132.In all the experiments conducted thus far, the FOXL2-p.Y186* variant behaviour did not differ from that of the WT, and further studies are underway to characterize its functionality inside the nucleus. On the other hand, given the importance of mitochondrial dynamics in both oocyte metabolism and tissue aging, our experimental data suggest that the FOXL2-p.E92* might eventually determine the onset of POI in the BPES-affected patients.

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GP220

Depletion of the primate-specific luteinizing-hormone receptor splice variant 'exon-6A' impairs LH-, but not hCG-mediated signaling in human primary granulosa cells

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Introduction
A primate-specific luteinizing hormone (LH) receptor (LHCGR)-variant was suspected to discriminate between maternal choriogonadotropin (hCG)- and fetal LH-functioning. It is the so-called "LHCGRex6A", truncated, intracellular receptor isoform produced by alternative cryptic exon stop-codons located between the 6th-7th out of 11 exons. Its function is unknown, although pseudohermaphroditism and 46-XY female-like phenotype were associated with *LHCGRex6A* mutations, in spite of intact *LHCGR* wild-type. LHCGR-6A was proposed as a key-mediator of hCG-signals in primates.
Aim
In order to address evolutionary issues related to LHCGRex6A, we evaluated the functions of this isoform in modulating LHCGR-driven LH- and hCG-signals *in vitro*.
Methods
Cell model is human primary granulosa lutein cells (hGLC), naturally expressing both the wild-type and LHCGRex6A, treated by siRNA for their selective depletion. siRNA efficacy was evaluated by qPCR, Western blotting and immunofluorescence, cell viability by MTT assay. Impact of LHCGRex6A on steroidogenic-signals was evaluated as LH- and hCG-dependent 2-h cAMP production by ELISA, 15-min CREB and ERK1/2 phosphorylation by Western blotting, 12-h *STARD1*- and *CYP19A1*-target gene expression by qPCR, 8-/24-h synthesis of progesterone by immunometric-assay. Forskolin-stimulated hGLC served as controls and data were normalized over cell number ($5x10^4$ cells-per-well).
Results
LHCGRex6A mRNA and protein analysis, and immunofluorescence under permeabilizing/*non*-permeabilizing conditions certified siRNA efficacy. Viability of siRNA- and mock-transfected hGLC confirmed experimental reliability. Equipotent, 500 pM LH and 100 pM hCG concentrations resulted in similar cAMP levels by mock-treated hGLC, while hCG induced 3-fold higher cAMP increase than LH in siRNA-treated hGLC (cAMP-LH = 14.0 ± 8.7 pmol/ml; cAMP-hCG = 33.1 ± 16.2; basal = 0.5 ± 0.3; means ± S.E.M.; Mann-Whitney's; $P < 0.05$; $n = 6$). Consistent with cAMP, hCG induced higher downstream pCREB activation than LH, while no different pERK1/2 activation was found, as well as *STARD1* and *CYP19A1* expression (ANOVA; $P \geq 0.05$; $n = 3$), reflecting the qualitatively different LH/hCG-specific signal. While no different 8-h LH-/hCG-induced progesterone response was found, 24-h hormone production were about 2-fold higher upon hCG than LH exposure of siRNA-treated hGLC (progesterone-LH = 35.7 ± 5.5 ng/ml; progesterone-hCG = 64.0 ± 11.3; basal = 24.2 ± 3.2; means ± S.E.M.; Mann-Whitney's; $P < 0.05$; $n = 5$). Controls provided similar results.
Discussion
LHCGRex6A depletion impaired LH-, but not hCG-specific steroidogenic-signal in spite of functional LHCGR-expression, suggesting evolutionary relevance of the receptor-variant functioning during fetal stages in primates. LHCGRex6A roles would be investigated in the not-readily available primate male testis cells, providing wider picture of LH/hCG co-evolution.

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GP221

The value of androstenedione and DHEA-S levels in diagnosis of polycystic ovary syndrome in young women

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Context
Polycystic ovary syndrome (PCOS) is a very common endocrinopathy affecting approximately 6–18% of women of reproductive age. It is also the most common cause of infertility due to anovulation. PCOS is characterized by menstrual disorders, polycystic or enlarged ovaries on ultrasound, but hyperandrogenism is the central feature of PCOS. Assessing of serum testosterone level (T) or free T is recommended by the guidelines in the diagnosis of PCOS. Diagnostic value of androstenedione is undetermined. Dehydroepiandrosterone sulfate (DHEA-S), an androgen nearly exclusively produced by the adrenals, is increased in many women suffering from PCOS, however its measurement is often omitted.
Aim
The aims of the study were:
1. to assess the frequency of increased level of testosterone (T), androstenedione (A) and DHEA-S in PCOS patients;
2. to examine the level of androgen suppression in low-dose (1 mg) night dexamethasone suppression test (LDDST) in PCOS patients.

Subjects and Methods
We analysed data of 195 young (median age 24.76 years) women, who were the patients of our Endocrinology Department, in whom PCOS was recognized with AES Criteria (2006) and T, A and DHEA-S level were measured. In $n = 104$ patients LDDST was performed.
Results
1. Increased T was found in $n = 61$ (31%) subjects and in $n = 15$ (8%) it was the only one elevated androgen (A and DHEA-S were within normal range).

2. Increased A was found in $n=97$ (50%) subjects and in $n=35$ (18%) it was the only one elevated androgen (T and DHEA-S were within normal range).
3. Increased DHEA-S was found in $n=77$ (39%) subjects and in $n=19$ (10%) it was the only one elevated androgen (T and A were within normal range).
4. LDDST revealed 33% decrease in the concentration of T, 45% decrease in the concentration of A and 41% decrease in the concentration of DHEA-S.

Conclusions

1. The value of A and DHEA-S measurement in the diagnostic process of hyperandrogenism in PCOS is underestimated.
2. In case of women with PCOS, a significant part of A and DHEA-S is produced by ovaries.
3. The measurement of A and DHEA-S concentrations is essential and useful in the diagnosis of hyperandrogenism in PCOS.

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GP222

Change in visceral fat and its relation with change in lipids in trans persons during hormonal therapy: results from a multicenter prospective study

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Introduction

Excess visceral adipose tissue (VAT) is strongly related to multiple cardiovascular risk factors such as dyslipidemia. Hormonal therapy (HT) in trans persons affects total body fat and body fat distribution, but the effect on VAT and its relation to changes in lipids is unknown. The aim of our study was to investigate the effect of one year HT on changes in VAT and its relation with changes in total cholesterol, HDL, LDL, and triglycerides after one year of HT.

Methods

In a multicenter prospective study at two university hospitals, 179 male-to-female trans persons (transwomen) and 162 female-to-male trans persons (transmen) underwent whole body dual-energy X-ray absorptiometry (Hologic Discovery A, Hologic Inc., USA) and laboratory measurements before and after one year of HT. Linear mixed models were performed to estimate changes over time and linear regression was used to examine the relation between changes in VAT with changes in lipids. Analyses were adjusted for age, body mass index (BMI), and smoking.

Results

In transwomen (median age: 29 years, IQR 23–43), VAT increased with 10 grams (range −289–251 grams, s.d.: 87) or 3% (95% CI 0;7), while abdominal fat increased with 13% (95% CI 9;18) and total body fat with 25% (95% CI 21;29). Changes in lipids per s.d. change in VAT were 0.2 mmol/l (95% CI 0.1;0.3) in total cholesterol, 0.1 mmol/l (95% CI 0.1;0.2) in LDL, 0.0 mmol/l (95% CI −0.1;0.0) in HDL, and 0.1 mmol/l (95% CI 0.0;0.2) in triglycerides. In transmen (median age: 24 years, IQR 21-33), VAT increased with 6 grams (range −331–179 grams, s.d.: 83) or 3% (95% CI −3;9), while total body fat decreased (−11%, 95% CI −13;−8) and abdominal fat did not change (−2%, 95% CI −6;2). Changes in lipids per s.d. change in VAT were 0.0 mmol/l (95% CI −0.1;0.1) in total cholesterol, 0.0 mmol/l (95% CI −0.1;0.1) in LDL, 0.0 mmol/l (95% CI −0.1;0.1) in HDL, and 0.1 mmol/l (95% CI 0.0;0.2) in triglycerides.

Conclusions

One year of HT resulted in large changes in total body fat, but in small mean changes in VAT, with a large inter-individual range in both transwomen and transmen. An increase in VAT was associated with small increases in total cholesterol and LDL in transwomen, but not in transmen.

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GP223

GHR ablation in the brain or in leptin receptor expressing cells causes metabolic effects during pregnancy

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Introduction

Pregnancy leads to extensive adaptations in the female's body, by changing the secretion and responses to several hormones. GH is required for fetal nutrition, growth during pregnancy and for mammary development and lactation, although its central effects are not completely clarified.

Aim

The aim of this study was to investigate whether central GH signaling regulates physiological and metabolic adaptations during pregnancy.

Methods

We produced mice carrying ablation of the GH receptor (GHR) either in neurons ($GHR^{flox/flox}/Nestin^{Cre}$) or in cells that express the leptin receptor ($GHR^{flox/flox}/LepR^{Cre}$). These females were mated and, when the first day of gestation was identified via the identification of the copulatory plug, they were individualized and further studied.

Results

Pregnant $GHR^{flox/flox}/Nestin^{Cre}$ females had higher food intake, weight gain, insulin sensitivity (ITT), and IGF-1 concentrations during pregnancy as well as lower adiposity, serum concentrations of insulin and leptin. During the lactation period, these females presented higher deposition of subcutaneous fat. The GHR deletion in leptin receptor cells also resulted in higher food intake and reduced adiposity in all evaluated periods. In addition, a better glucose tolerance, higher insulin sensitivity and lower serum concentrations of insulin and leptin were also observed in pregnant $GHR^{flox/flox}/LepR^{Cre}$ females.

Conclusion

These results indicate that GH plays a role in metabolic control during gestation. Other experiments are being conducted to better clarify the mechanisms involved.

Keywords: energy balance, gestation, growth hormone, cytokine signaling.
Financial support: CNPq e FAPESP.

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Thyroid Cancer - Diagnostics & Treatments

GP224

Association between preoperative thyrotrophin and clinicopathological and aggressive features of papillary thyroid cancer

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Aim

We aimed to investigate the relation between preoperative serum thyrotrophin (TSH) and clinicopathological features in patients with papillary thyroid carcinoma (PTC) and microcarcinoma (PTMC).

Methods

Patients who underwent thyroidectomy and diagnosed to have benign nodular disease or PTC/PTMC in our clinic were evaluated retrospectively. Patients with a previous history of thyroid surgery, patients using antithyroid medications or thyroid hormone and patients with tumors known to be unresponsive to TSH were excluded. Histological variants of PTC were classified as nonaggressive (classical/conventional and follicular variants), aggressive (tall cell, diffuse sclerosing and columnar variants) and other variants.

Results

Data of 1632 patients were analyzed. Histopathological diagnosis was benign in 969 (59.4%) and malignant in 663 (40.6%) patients. Preoperative median serum TSH was significantly higher in malignant compared to benign group (1.41 IU/dl vs 0.98 IU/dl, $P<0.001$). Malignancy risk increased gradually as going from hyperthyroidism to euthyroidism and hypothyroidism (20, 40.6 and 59.1%, respectively, $P<0.05$). Serum TSH was lowest in benign nodular disease, higher in PTMC and highest in PTC ($P<0.001$). This was also true when patients with positive antithyroid peroxidase/antithyroglobulin and with lymphocytic thyroiditis were excluded from the analysis ($P<0.001$). Serum TSH was higher in patients with bilateral tumor, capsular invasion and lymph node metastasis (LNM) compared to patients with unilateral tumor, without capsule invasion and without LNM, respectively ($P=0.036$, $P=0.002$ and $P=0.001$, respectively). Patients with aggressive variant PTC had higher serum TSH than nonaggressive ones ($P<0.05$).

Conclusion

Preoperative serum TSH was associated with increased risk of thyroid cancer and LNM regardless of autoimmune thyroid disease. With the present study, for the

first time, we showed higher preoperative TSH in aggressive variants of PTC compared to nonaggressive ones.

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GP225

Germline mutations in *KIF1B* gene in two families with familial non-medullary thyroid cancer (FNMTC)

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Introduction
Familial non-medullary thyroid cancer(FNMTC) represents 3–9% of thyroid cancer cases. Although the susceptibility genes for syndromic FNTMC are known, most cases of FNMTC are nonsyndromic and the genetic causes are unknown.
Patients and methods
We conducted a multicenter study to identify a candidate susceptibility gene for nonsyndromic FNTMC. We collected blood specimens, clinical and pathological data from 38 kindreds with FNMTC (32 with two affected members, six with ≥ 3 affected members). Genomic DNA was extracted from peripheral blood samples and Whole-Exome sequencing (WES) was performed in 10 affected individuals from four kindreds with at least three cases of FNMTC in each kindred. We filtered and identified the germline SNPs and INDELs using Haplotype Caller using the GATK package. We identified and validated the likely pathogenic variants (LPV) by Sanger sequencing in 38 kindreds and in our own control group (50 healthy subjects).
Results
Sixty-eight percent were women, with a mean age at diagnosis of 42.6 ± 13.6 years. 90.4% had classic papillary thyroid cancer, 26% were bilateral and 46% were multifocal. Among genes with LPV and population frequency of $<5\%$, we identified two novel germline heterozygous mutations in kinesin family member1B gene (*KIF1B)* in two kindreds. In the first family, five of five affected members presented a mutation c.2680G$>$A (p.V894M) in exon 24 and three of four affected members in the other family had a c.2480C$>$T (p.T827I) mutation in exon 23. We believe that the remaining member could be a phenocopy considering the high prevalence of thyroid cancer. Both LPVs are described in ExAc database with population frequencies of $<0.2\%$. Importantly, we didn't find the V894M *KIF1B* variant in our control group. We didn't test T827I variant in control group as it was already described as a very rare variant (not present among 270 controls of diverse ethnic backgrounds). *KIF1B* is in the chromosomal region 1p36.22 and encodes a motor protein that transports mitochondria and synaptic vesicle precursors. Several studies suggested *KIF1B* as a potential tumor suppressor gene particularly in neuroblastomas.
Conclusions
We identified two families with FNMTC presenting two novel or rare germline variants in *KIF1B* gene. Further studies are needed to establish the potential pathogenic impact of these genetic changes, as well as its involvement as a possible risk factor to develop FNMTC.
Collaborators: R. Alfayate, S. Martínez, F. Hanzu, S. Chicharro, C. Villabona, J. Otero, A. Simó, M.C. Vilardell, A.M. Gutiérrrez, E. Pizarro, A. Sitges, C. Zafón, A. Ortiz, P. Casano, J.J. Díez, P. Iglesias, J. Biarnés, M. Recasens, R. Casañ.

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GP226

Significant acceleration in dynamics of medullary thyroid cancer markers concentration – report of 26 cases

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Calcitonin and carcinoembryonal antigen are biochemical markers of medullary thyroid carcinoma (MTC). Assessment of the dynamics of their serum concentration allow for calculation of their doubling times that are independent risk factors for overall survival and progression-free survival in MTC. It is generally accepted that the dynamics and the doubling times remain stable during follow-up.
Aim
The aim of the study was to retrospectively verify the stability of calcitonin and CEA doubling times during follow-up in a population of 1650 medullary thyroid carcinoma patients followed-up in a single center.
Results
We found and present 26 patients in whom during follow-up significant change in marker's doubling time was observed significantly influencing their prognosis and treatment.
Conclusion
We should not excessively delay follow-up visits in MTC patients with decreasing, stable or slowly increasing markers concentration as there is possibility of revealing rapidly-progressing clone. It would be beneficial to test the genetic background leading to reproductive or survival advantage of that clone in progressively observed patient.

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GP227

The adverse effect of radioactive iodine therapy on bone marrow for differentiated thyroid cancer patients

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Aims
Side effects of large dose of radioactive iodine (RAI) therapy for well-differentiated thyroid carcinoma are noted.There were insufficient data regarding bone marrow suppression and inflammatory response in patients with thyroid cancer who received RAI therapy in Asia;
Patients and methods
We performed the study at the Chang Gung Memorial Hospital in Keelung, Taiwan. Patients with papillary or follicular thyroid cancer who received more than 2.6 GBq (70 mCi) RAI were enrolled in this hospital based study. We evaluate the renal function, serum inflammatory marker and bone marrow suppression before and 1 week after RAI treatment. In addition, these analyses were also performed between thyroxine withdrawl and recombinant human thyrotropin (rh-TSH) injection groups.
Results
There have been 101 patients who completed the blood test. The WBC count decreased 1 week after radioiodine treatment compared with that before RAI treatment (6307 ± 1527/ul vs 5476 ± 1439/ul, $P < 0.001$). Among 72 patients with thyroxine withdrawl and 29 patients with rh-TSH injection, the WBC count was lower in patients with thyroxine withdrawl than those with rh-TSH injection although there is not statistically significant ($P = 0.080$). The serum creatinine level is significantly higher in patients with thyroxine withdrawl than those with rh-TSH injection ($P < 0.001$). There is no any difference regarding RBC count, platelet count and serum CRP level between thyroxine withdrawl and rh-TSH groups.
Conclusions
The data gives useful information in thyroid cancer patients taking high dose of RAI treatment, and helps to suggest dose adjustment concerning about radiation safety for the patients.

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GP228

Familial non-medullary thyroid carcinoma. Are we facing a different entity?

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Background
Familial non medullary thyroid carcinoma (FNMTC) is a not very well known histopatologic entity. Nowadays there are controversial publications about his aggresiveness and prognosis
Objective
To know the clinical outcomes and histopathological characteristics of our patients with FNMTC and to compare them with a cohort of patients with sporadic non medullary thyroid carcinoma (CDT).
Methods
We conducted a retrospective descriptive study including 55 familial non medullary carcinoma patients belonging 27 families diagnosed beetwen 1983 and 2017. Every family had two or more first degree relatives with FNMTC. They were compared with an aleatory sample of our cohort of patients with sporadic differentiated thyroid carcinoma (DCT) (750 cases).
Results
25 (92.6%) families had 2 members affected. 7 (21.21%) families had one member diagnosed with papillary microcarcinoma. 70.9% were women. Median age at diagnosis was 45.9 (37.8–56.5) years. 15 (55.56%) families were siblings and 13 (48.15%) parent-child. The age of presentation between parents-child show a significative difference of 20 (15–27) years ($P<0.05$). Histologically, 85% were papillary, and 15% were follicular. Multifocality was observed in 38%,19.6% showed extrathyroid extension and 6% surgical margins affected. Staging at diagnosis revealed 67.3% of patients were at stage I, 7.7% stage II, 19.2% stage III, and 1.9% at stage VIb, the 3.8% of patients presented metastasis at diagnosis. Total thyroidectomy was carried in 93.3% patients, central neck cervical dissection was added in 51.1% and the 10.6% recieved also a lateral neck linphadenectomy. 55 (98.21%) recieved radioactive iodine remmant ablation. More than 1 RAI were applied in 9 (21.2%) patientes. Median radiactive activity recieved was 105 (100–118) mCi. After a median follow-up of 4 (1–8) years, excellent response was observed in 86.4%, indeterminated response (biochemical or estructural) in 4.5% and incomplete response in 4.5%. 2 cancer related deaths were observed in our cohort. We haven't found any mayor prognosis difference between our FNMTC and our sporadic DTC cohort. A higher presence of aggresive histology tumors was observed in the FNMTC cohort (10.7% Vs 4%, $P<0.05$).
Conclusions
We haven't found significative histopathological, survival or prognosis differences between our FNMTC and sporadic DCT cohorts. Although we have a wide series, families with three affected members are under represented. We have to consider the probability of sporadic disease in the pedigrees with only two members affected. Earlier age presentation in second generation patients was observed in our cohort.

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GP229

Is thyroid nodule size a factor to consider when deciding for fine-needle aspiration procedure?

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Introduction
Fine-needle aspiration (FNA) is the most accurate diagnostic approach for determining thyroid nodule malignancy. Most nodules are benign, therefore, only suspicious ones require FNA. In 2017 American College of Radiology proposed a scoring system – Thyroid Imaging, Reporting and Data System (TI-RADS) for identifying clinically significant malignancies. Whether a nodule requires FNA depends on various criteria, one of which is the size. The aim of this study was to determine whether size is an important factor in deciding the necessity for FNA.
Methods
A total of 288 ultrasound images of patients with thyroid nodules were analysed. The nodules were scored, measured and assigned to one of five TI-RADS levels (TR): TR1 – benign, TR2 – not suspicious, TR3 – mildly suspicious, TR4 – moderately suspicious, TR5 – highly suspicious. The results were compared with histology findings.
Results
219/288 (76%) benign and 69/288 (24%) malignant thyroid nodules were verified histologically. Nodules were distributed as follows: TR1 – 17 (5.9%), TR2 – 27 (9.4%), TR3 – 72 (25.0%), TR4 – 126 (43.8%), TR5 – 46 (16.0%). The mean size of measured nodules was 2.05 ± 1.02 cm. In categories TR1 and TR2 100% of nodules were benign according to FNA. In TR3 68/72 (94.4%) of nodules were benign and 4/72 (5.6%) malignant, 38/72 (52.7%) <2.5 cm in size and 34/72 (47.22%) – ≥ 2.5 cm. None of the malignant nodules in TR3 were ≥ 2.5 cm. Negative correlation ($r_s = -0.298$, $P=0.011$) was found between size and malignancy. In TR4 93/126 (73.8%) of nodules were benign and 33/126 (26.2%) malignant, 59/126 (46.8%) <1.5 cm in size and 67/126 (53.2%) – ≥ 1.5 cm. Size of ≥ 1.5 cm had sensitivity of 39.39%, specificity of 41.94%, positive predictive value (PPV) of 19.40%, negative predictive value (NPV) of 66.10% and accuracy of 41.27%. No significant correlations between size and malignancy in TR4 were found. In TR5 14/46 (30.4%) of the nodules were benign and 32/46 (69.6%) malignant, 11/46 (23.9%) <1 cm in size and 35/46 (76.1%) – ≥ 1 cm. Size of ≥ 1 cm had sensitivity of 68.75%, specificity of 7.14%, PPV of 62.68%, NPV of 9.09% and accuracy of 50%. Negative correlation ($r_s = -0.304$, $P=0.04$) was found between size and malignancy.
Conclusion
Our study shows that thyroid nodule size threshold suggested in TI-RADS levels TR3 – TR5 is not reliable in predicting malignancy risk. Therefore, we think that nodule size is neither a good predictor of malignancy nor a good indicator for FNA.

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GP230

Peptide receptor radionuclide therapy in patients with medullary thyroid carcinoma: predictors and pitfalls

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Aim
To evaluate the effectiveness of Peptide Receptor Radionuclide Therapy with ^{177}Lu-octreotate (PRRT) for medullary thyroid carcinoma (MTC).
Background
There are few therapeutic options for progressive metastatic MTC. The Erasmus MC Center for Neuroendocrine Tumors has been at the forefront of developing PRRT for neuroendocrine tumors. PRRT has also been suggested to be a useful treatment for MTC, but evidence is very limited.
Methods
Retrospective evaluation of results of our ten years' experience with PRRT treatment in a highly selected group of MTC patients with progressive disease or refractory symptoms. In addition, a retrospective evaluation of uptake on historical ^{111}In-DTPA-octreotide scans was performed in patients with detectable tumor load >1 cm.
Results
Over the years, ten MTC patients were treated with PRRT. Forty percent of patients (4/10) showed stable disease at first follow up (8 months after start of therapy) whereas the other six were progressive. Patients with stable disease had the combination of both a high uptake on ^{111}In-DTPA-octreotide scan (grade $\geqq 3$; more than liver) and a clear somatostatin receptor type 2a (SSTR2a) expression on tumor by immunohistochemistry. Retrospective evaluation of historical ^{111}In-DTPA-octreotide scans of 35 non-treated MTC patients revealed uptake less than liver (Grade 1) in the vast majority of patients 31/35 (89%) with uptake similar as liver (Grade 2) in the remaining 4/35 (11%).
Conclusions
PRRT using ^{177}Lu-octreotate was only effective in the patients that had the combination of high uptake on ^{111}In-DTPA-octreotide scan ($>$liver) and in which the pathology report showed clear SSTR2a expression. This high uptake was only present in a very limited number of patients, suggesting that this treatment can only be considered for a highly selected group of MTC patients.

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GP231

Related recurrence factors in a Spanish cohort of differentiated thyroid carcinoma. Cadit-CAM Study

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Background and objective
Incidence of differentiated thyroid cancer (DTC) is increasing but not its mortality. Knowing recurrence factors is essential to plan its treatment. Recurrence related factors in our area were reviewed and compared with ATA risk stratification system.
Patients and Methods
The Cadit-CAM study was designed to evaluate characteristics of patients diagnosed of DTC in Castilla La Mancha, a region in the central part of Spain, during 15 years (from 2001 to 2015). The cohort in Cadit-CAM study included 1434 patients from seven regional hospitals. The variables analyzed were: sex, age, size, histopathologic subtype, multifocality, involved lymph nodes, lymphadenectomy, extrathyroidal extension, metastases at diagnosis (MTS), intentionally total thyroidectomy (ITT), anti-thyroglobulin antibodies with rising titers (TG-Ab). Treatments and evolution of patients who recurred were also evaluated.
Results
324 patients recurred (23%), being 82% ATA high risk (71 patients), 33% ATA intermediate risk (160) and 9% ATA low risk (93). Factors independently related to recurrence were MTS with OR 46.7 (95% CI 13–165); TG-Ab 4.86 (2.4–9.9); positive lymph nodes 4.38 (2.7–6.9), multifocality 2.2 (1.59–3.05), extrathyroidal extension 2.09 (1.4–3.1), size >3 cm 1.83 (1.23–2.72); male 1.64 (1.15–2.32). Those not statistically related to recurrence were ITT 1.33 (0.82–2.1); age 0.99 (0.98–1); lymphadenectomy 0.8 (0.5–1.28) and histology 0.7 (0.34–1.41). Recurrence treatments were: Iodine-131 (56%); surgery (31%), both (23%), kinase inhibitors (5%), observation (8%), and palliative surveillance, radiotherapy, cementation, and chemotherapy (<1%), For patients with recurrence the outcome at the end of the follow up was: 26% alive without evidence of disease, 24% alive with structural disease, 27% indeterminate or biochemically incomplete response and 10% died for DTC
Conclusion
23% of the patients with DTC recurred. Recurrence poor prognosis factors were MTS, TG-Ab, involved lymph nodes, multifocality, extrathyroidal extention, tumor size and male sex. ATA Risk stratification predicts recurrence, however two third of these patients were in ATA intermediate and low risk groups.

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GP232

Imaging in clinical research devoted to medullary thyroid carcinoma: a systematic meta-analysis

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Background
We analyzed the role of imaging in the identification of medullary thyroid carcinoma (MTC) metastases and in the assessment of treatment response of the patients in clinical trials and research studies devoted to MTC.
Materials and methods
A search for published studies devoted to MTC from January 2010 to August 2017 was performed.
Results
Fifteen studies published in peer review journals that evaluated the effects of sorafenib, cabozanitinib, vandetanib and sunatenib were analyzed. In a pooled cohort of 922 patients with advanced MTC, metastases in lymph nodes were found in 70%, liver in 63%, lungs in 54% and bone in 44%. Eleven out of 15 publications described imaging modalities to assess metastases. Of those, all 11 reported the use of computed tomography (CT), five used magnetic resonance tomography (MRI), in two studies bone scintigraphy. Only one study reported the exploratory use of positron emission tomography/computed tomography (PET/CT) with 18-fluorodeoxyglucose and dynamic contrast-enhanced MRI. No study used PET/CT with fluorine-18-dihydroxyphenylalanine (18-F-DOPA). Imaging timing for initial and follow-up varied. All studies used Response Evaluation Criteria In Solid Tumors (RECIST) to assess the response to treatment. Cumulative analysis showed that overall complete response was diagnosed only in one case (0.3%); partial response in 30%, stable disease was noted in 60% and progressive disease in 10% without statistical significance between the studies and types of treatment used. A meta-analysis showed the limited use of modern imaging modalities for MTC and the lack of detailed description of radiological findings in all analyzed publications. There is no consensus and protocol on the radiological evaluation of MTC patients. New advanced imaging techniques (such as diffusion-weighted MRI, dynamic contrast MRI, PET/CT with 18-F-DOPA, 69-GA DOTATATE etc), which have high diagnostic value in oncology, were not used in presented studies.
Conclusion
1. Modern imaging modalities have limited use in clinical research and trials devoted to MTC.
2. Development and introduction of new imaging protocols will be very helpful for further research of new treatment modalities and comparison of the efficiency of different treatments.
3. New advanced imaging techniques may be helpful in advanced MTC and therefore should be evaluated.
4. RECIST does not adequately reflect changes related to treatment in MTC, therefore it should not use in the future.

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GP233

Molecular profiling of a large papillary thyroid cancer series followed at a single center: data on mutation density, heterogeneity and phenotype-genotype correlations

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Recent advances in the molecular classification of papillary thyroid cancer (PTC) have improved the diagnostic work-up and the care of patients with thyroid nodules and cancer, highlighting the need to routinely add information on the genetic pattern to the classification of cancer. The genomic background of a large series of 208 PTCs followed at a single Center was analysed by a custom MA genotyping platform (PTC-MA), which allows the simultaneous detection of 19 genetic alterations including point mutations and fusions in a sensitive, fast and economic way. The 74% of the cancers analysed has been genetically classified, being *BRAF*^{V600E} variant and *TERT* promoter mutations the most frequent alterations, followed by *RET/PTC* fusions. Fusions were significantly more frequent in younger ages, while *TERT* associated with older patients. Interestingly, in 20% of cases two or more mutations were found. In particular, a *TERT* promoter mutation was associated with *BRAF* and *RAS* mutations in 28.7 and 14.2%, respectively, and the co-occurrence of a fusion with ≥ 1 point mutation/s was also observed. In the majority of cases, allelic frequencies were consistent with the presence of the heterozygous mutation in virtually all the neoplastic cells. Nevertheless, in a minority of cases, mutations were detected by the PTC-MA assay even if present at low allelic frequencies indicating a tumor heterogeneity. A significant correlation of aggressive features was found with mutation density, but not with the allelic frequencies of driver oncogenes. The genotype-phenotype correlation revealed that aggressive clinical characteristics were more frequent in mutated cases, and the strong cooperative role of coexisting *BRAF*^{V600E} and *TERT* promoter mutations in the development of a group of PTCs displaying the worst clinicalpathological features was confirmed. In conclusion, a large monoinstitutional series of PTCs was fully genotyped by means of a cost and time-effective customized panel, revealing interesting data and implying the actual prospective to routinely include it in thyroid cancer classification, in view of a personalized therapeutic approach.

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GP234

Title Evaluation of the CCK-2-receptor agonist 177Lu-PP-F11N for peptide receptor radionuclide therapy (PRRT) of medullary thyroid carcinoma - First results of a phase 0 'Lumed' Study

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Objectives
There is still an unmet need for an effective systemic therapy for advanced medullary thyroid carcinoma (MTC). Targeting the cholecystokinine-2 (CCK-2) receptor with radiolabelled gastrin analogues is a potential approach for radionuclide therapy, as MTC expresses CCK-2 receptors at a high incidence and density. Unfortunately, kidney and bone marrow toxicity precluded therapeutic applications of CCK-2 receptor specific compounds until now. The aim of this prospective study is the feasibility testing of targeting CCK-2 receptors with the novel 177Lu labelled gastrin analogue PP-F11N [DOTA-(DGlu)6-Ala-Tyr-Gly-Trp-Nleu-Asp-PheNH2]in six patients with metastasized MTC (ClinicalTrials.gov: NCT02088645).
Methods
Six patients received two injections of 1 GBq 177Lu-PP-F11N, one injection without and the other one with additional Physiogel infusion for nephroprotection. Planar scintigraphy and SPECT/CT scans were performed at several time points for up to 72 h post injection in order to calculate tumor- and organ doses using 3D voxel-based dosimetry. Blood samples were taken for the purpose of bone marrow dose calculation. ECG, blood count and blood chemistry were measured up to 12 weeks after the second administration of 177Lu-PP-F11N in order to evaluate adverse events.
Results
Apart from self-limiting flushing, nausea and vomiting (grade 1 according to CTCAE version 4.0), there were no adverse reactions observed. In all patients, radiotracer uptake in tumor tissue was visible in the scintigraphic images. Furthermore, uptake in the kidneys, stomach and colon was visible. The radiation doses to the tumors and organs were calculated for the three patients: dose range in tumors was between 1 and 1.5 Gy/GBq, dose range in kidneys 0.045–0.075 Gy/GBq (without Physiogel) and 0.07–0.15 Gy/GBq (with Physiogel), resulting in tumor-to-kidney dose ratios between 13.3 and 27.3. Calculated bone marrow doses were 0.01–0.02 Gy/GBq, resulting in tumor-to-bone marrow dose ratios between 50 and 150.
Conclusions
The administration of the new CCK-2 receptor ligand 177Lu-PP-F11N was safe. Visualization of metastasized/recurrent disease in all patients proves that the principle of CCK-2 receptor targeting of MTC with this new radiopharmaceutical is feasible. Preliminary results of the 3D voxel-based dosimetry in the first three analyzed patients indicated tumor doses that could enable radionuclide therapy. Dosimetry results for kidneys and bone marrow revealed low organ doses as well as excellent tumor-to-kidney and tumor-to-bone marrow ratios. Further studies will be necessary to evaluate the theranostic potential of 177Lu-PP-F11N in patients with MTC.

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GP235

Does body mass index influence the clinical stage, treatment response and course of the disease in patients with differentiated thyroid cancer?

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Introduction
Obesity is a serious health problem worldwide, especially in well developed countries. It is a cause of various diseases, including thyroid cancer. The relationship between obesity and prognostic factors of thyroid cancer is uncertain.
Aim of the study
Evaluation of relationship between the body mass index (BMI) and clinicopathological features increasing the risk of poor clinical course, treatment response and clinical outcome in patients with differentiated thyroid cancer (DTC).
Material
The study included 1,181 patients with DTC (88% women and 12% men) who were treated at a single center from 2000 to 2016, who underwent retrospective assessment of BMI and clinicopathological features before surgery. The relationship between clinical features of treatment response (excellent, indeterminate, biochemically incomplete, structurally incomplete) or final status of the disease (remission, persistent disease, death) and BMI was evaluated. Patients were stratified according to BMI (underweight, normal weight, overweight and obesity according to World Health Organization classification). Statistical analysis was performed using univariate and multivariate logistic regression analysis.
Results
Median follow-up was 7.7 years (1–16 years). BMI did not affect the response to treatment or outcome of the disease (remission, persistent disease, death). Obesity was more prevalent in men ($P=0.033$) and was more common in patients ≥ 45 years of age ($P=0.001$). We found statistically significant relationship of advanced TNM stage (III-IV) with increases in BMI ($P=0.029$), however this association disappeared after adjusting for age of ≥ 45 years ($P=0.832$).
Conclusions
Obesity in our study is not associated with more aggressive clinicopathological features of cancer, it is not a risk factor for higher clinical stage of cancer, it is not a prognostic factor for poorer treatment response and clinical outcome in DTC patients.

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Thyroid Cancer - Translational

GP236

Neural stem cells expressing cytosine deaminase and interferon-β suppressed the growth and metastasis of anaplastic thyroid cancer cells

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In this study, human neural stem cells (hNSCs) were used to cancer treatment strategy for anaplastic thyroid cancer (ATC) owing to their tumor tropic properties. Cytosine deaminase (CD) can convert a prodrug, 5-fluorocytosine (5-FC), to drug, 5-fluorouracil (5-FU), which inhibits tumor growth through DNA synthesis inhibition. Also, IFN-β expression suppresses tumor growth by apoptotic process. Then, we investigated tumor inhibition effect of hNSCs *in vitro* and *in vivo*. We currently studying on a xenograft *in vivo* model, SNU-80 cells (2.0×10^7cells/mouse) were injected subcutaneously (s.c.) after mixed with 1:1 volume ratio of Matrigel (BD Biosciences, Bedford, MA, USA) into the back of the mice. When the tumor volume reached at 150–200 mm^3, CM-DiI pre-labeled hNSCs were injected subcutaneously closed to the tumor mass. After SNU-80 cells and hNSCs injection, 5-FC (500 mg/kg per day) injected every day for 21 days to Intraperitoneal injection (i.p.). In trans-well migration assay, HB1.F3.CD and HB1.F3.CD.IFN-β cells selectively migrated to SNU-80 cells because of its tumor-tropic properties. Engineering NSCs were attributed to chemo attractant factors like uPAR, CXCR4, SCF and VEGFR2 secreted by SNU-80 cells. Also when co-cultured with HB1.F3.CD and HB1.F3.CD.IFN-β cells, SNU-80 cell viability was reduced in presence of 5-FC. In this study, we proved the hNSCs expressing CD (HB1.F3.CD) and IFN-β (HB1.F3.CD.IFN-β) genes therapeutic effect. As a result, hNSC therapy with prodrug 5-FC may helpful for the treatment of human anaplastic thyroid cancer. Furthermore, we are currently studying on a xenograft *in vivo* model to prove that selective anti-tumor effect of hNSCs.

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GP237

Comparison in survival of the seventh and eighth editions of the American Joint Commision on Cancer in a Spanish cohort of differentiated thyroid carcinoma: Cadit-CAM Study

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Background and objective
The AJCC-TNM system is optimized to predict survival in patients with cancer. Since January 2018, the new eighth edition of this staging system will be used to classify patients diagnosed of differentiated thyroid carcinoma (DTC). This study aims to compare the seventh and eighth editions of the AJCC-TNM system in a Spanish Cohort of DTC.
Patients and Methods
The Cadit-CAM study was designed to evaluate characteristics of patients diagnosed of DTC in Castilla La Mancha (CAM), a region in the central part of Spain, during 15 years (from 2001 to 2015). The cohort in Cadit-CAM study included 1434 patients from seven hospitals. Staging criteria for the seventh and eighth editions were applied to the cohort. Disease Specific Survival (DSS) were calculated using the Kaplan-Meier method. Multivariate Cox proportional hazards model were used to estimate the association of each stage with survival in both editions.
Results
1426 patients were analyzed, 77% were women, with a mean age at diagnosis of 48.3 (15.6) years (y) and a mean follow up period of 5.8 (3.9) y, 92% papillary carcinomas. When TNM-8 was applied 26.1% of the patients were down-staged. In patients with $<$ 55 years at diagnosis (n: 947) 15.3% were reclassified and in patients $>=$55 years at diagnosis (N: 479) 50.1% were downgraded. The 10-years DSS rates in TNM-7 I, II, III and IV stages were 99.9, 95.7, 98.7 and 49.9% respectively. The 10-years DSS rates in TNM-8 stages were 99,8% (I), 89,1% (II), 42,6% (III) and 39,0% (IV) respectively.
Conclusion
A significant number of patients with DCT were down-staged from the seventh to the eighth edition in this cohort of Spanish patients. There was greater separation of survival curves based on disease stage using the eighth edition.

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GP238

Carrying mutations truncating CHEK2 protein predisposes to thyroid neoplasms – preliminary report

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Introduction
CHEK2 gene is one of the genes in the DNA repair complex. Dysfunction of genes in this complex leads to genomic instability and is regarded as a cause of tumorigenesis. CHEK2 mutations spectrum was assessed in many populations, including polish one. The most common are mutations truncating CHEK2 protein (1100delC, IVS2+1G>A, del5395) and a missense I157T CHEK2 mutation. Literature data indicate that mutations truncating CHEK2 protein lead to a five-fold increased risk of papillary thyroid cancer.
Aim
The aim of the study was to evaluate the relation between CHEK2 protein truncating mutations and prevalence of nodular goiter and thyroid cancer.
Material and methods
62 women, aged 25–60 years (average 42.5 years), with 1100delC, IVS2+1G>A and del5395 mutations of CHEK 2 gene were enrolled into the study. Thyroid ultrasound was performed with Aloka equipment with 7.5 MHz probe and blood sample was drawn to perform genetic tests. RFLP-PCR technique was used to detect IVS2+1G>A mutation, PCR to detect del5395 mutation and ASO-PCR using specific starter for an allele with single nucleotide deletion to detect 1100delC. Positive results of RFLP-PCR and ASO-PCR were subsequently verified by DNA sequencing.
Results
Among 62 women, 37 (59.7%) were diagnosed with nodular goiter and 25 (40.3%) had no thyroid lesions. In the group with nodular goiter 25 subjects (67.6%) underwent fine-needle aspiration biopsy (FNAB), 5 are planned for FNAB and 7 (18.9%) have not been qualified to FNAB because of too small dimensions of thyroid lesions and no sonographically suspicious features. Analyzing the group of 32 subjects (25 with FNAB and 7 without FNAB because of no indications), in 4 (12.5%) papillary thyroid cancer was initially diagnosed and afterwards confirmed with postoperative histopathological examination, 27 (84.4%) had benign lesions (20 had group II in The Bethesda System and in 7 basing on ultrasound features) and 1 (3.1%) the result was undetermined (group III).
Conclusions
1. Prevalence of nodular goiter in the study group was comparable to the general population.
2. Prevalence of papillary thyroid cancer in patients with nodular goiter carrying CHEK2 gene mutations was three-fold higher than prevalence of this cancer in general population.

Our preliminary conclusions may be redefined after performing thyroid diagnostics in more women carrying CHEK2 gene mutations.

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GP239

The capability of the Bethesda System Reporting for Thyroid Cytopathology (TBSRTC) in identifying of thyroid carcinoma

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Aim
To assess the accuracy of the TBSRTC in verification of thyroid carcinoma in the region of Moscow county.
Material and methods
A retrospective study of data from electronic medical notes of 1,675 patients who underwent fine needle aspiration biopsy of nodular thyroid glands in 2016. The cytological conclusion was evaluated in accordance with the TBSRTC. In cases of surgical treatment (thyroidectomy or hemithyroidectomy) the cytological diagnosis was confirmed by morphology studies and then grouped into the following categories: malignant and benign. Specificity, sensitivity, PPV and NPV were calculated with Microsoft Excel 2016.
Results
The frequency distribution of Bethesda categories in the cohort studied was: 112 (6.7%) for category I, 1432 (85.5%) for II, 7 (0.42%) for III, 90 (5.4%) for IV, 11 (0.7%) for V, 23 (1.3%) for category VI. Surgical treatment was performed in 115 cases (6.9%) in patients: 1 from 112 pts in category I; in 36 from 1432 pts in category II; in 3 of 7 pts in category III; in 46 from 90 pts in category IV; in all 11 pts in category V; in 18 from 23 pts in category VI. Thyroid carcinoma was confirmed in 46 (40.0%) cases of surgical treatment group: 0 pts in category I, in 3 (8.3%) pts in category II, in 2 (66.7%) in category III, in 14 (30.4%) in category IV, in 9 (81.8%) pts in category V, in 18 (100%) pts in category VI. The sensitivity in detecting malignant neoplasms for categories IV+V+VI was 89.1% (95% CI 77–95.3%); specificity for category IV was 46.3% (35.1–58%); for category V 97.1% (90–99.2%); for category VI 100% (94.7–100%). PPV for category IV was 30.4 (19.1–44.8%); for category V 81.8 (52.3–94.9%); for category VI 100% (82.4–100%). NPV for category IV was 53.6 (42–65%); for category V 64.4 (54.9–73%); for category VI 71.1 (61.5–79.2%).
Conclusion
The highest PPV and NPV were noted in category VI, the lowest value was found in category IV. Sensitivity for categories IV+V+VI was high and majority of malignant cases were identified due to cytological investigation. More studies are needed to separate malignant nodules from benigh in category IV.

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GP240

Orthotopic PDX Mouse Model of humanprimary Undifferentiated/ Anaplastic thyroid carcinoma

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Undifferentiated/Anaplastic thyroid carcinoma (ATC) is one of the most aggressive and deadly cancers. It is characterized by loss of thyroid expression markers and no response to conventional treatments. ATC incidence is low representing $<2\%$ of all thyroid carcinomas. This, together with its high mortality, makes difficult the development of clinical trials. In our previous works, we have developed a system to culture patient-derived thyroid cancer cells (h7H) that is a good way to test new therapies. On the other hand, cell cultures don't maintain the complete tumor environment and 3D structure of a human cancer. Orthotopic patient-derived anaplastic tumors (PDX) in mouse could provide a relevant model to study the structural disease, test best culture-selected therapies and perform precision medicine.
Methods
We designed a retrovirus construct encoding a chimera Luciferase-IRES-mCherry. A patient-derived ATC primary culture grown in h7H was infected with this retrovirus. Cells were orthotopically implanted in NOD-SCID immune deficient mice through neck surgery using an in house developed minimally disruptive approach and a Hamilton device. During the following weeks, mice were followed *in vivo* using an IVIS imaging system and through neck palpation, measuring neck masses with a precise calliper. A small group of mice was sacrificed 5 weeks after injection. A second group of mice were sacrificed at week 10. The last group of mice was sacrificed at week 14. At autopsy, all organs were observed and neck tissue collected for pathology analysis, staining with relevant markers and final precise dimensions.
Results
All avatar mice presented a growing neck cancer with aggressive characteristics in the luminescent assay (growing intensity, neck invasion, displacement of neck structures). The pathology revealed a cancer with similar characteristics to human ATC (high mitotic index, thyroid, nerve and muscle invasion, vascular invasion, fibrin deposition, aberrant mitotic figures, giant cells, pleomorphic nuclei and multinucleated cells). Necrosis appeared after the 10th week of evolution. p53, Ki67, TTF1 and PAX8 markers were positive as expected using conditions similar to the ones in patients' samples.
Conclusions
Appropriate culture conditions are essential to obtain phenotype maintenance in patient-derived primary cultures. Our results showed local tumor growth and progression within the first week after cell implantation and its progression was followed along the weeks as big neck masses. We have obtained an avatar model that allows some pre-clinical studies during fourteen weeks. This model could offer a new tool for studying the biological mechanisms involved in ATC and test new therapies.

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GP241

Detection of lncRNAs in thyroid nodule as new tool for tumor diagnosis: analysis by Droplet Digital PCR in Fine Needle Aspiration biopsy

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Background
Differentiated Thyroid Carcinomas (DTC) represent more than 90% of thyroid tumors with good prognosis and long survival. Currently, patients with intermediate/high risk nodule as assessed by cytological staging may undergo surgery. According to ATA 2017 guidelines, all patients presenting thyroid nodules with suspicious ultrasound features (hypoechoic pattern, irregular margins, microcalcifications, etc.) and cytopathology TIR3B, TIR4 or TIR5 according to 2014-SIAPEC classification may undergo to surgery. However, not all nodules are malignant: about 25–30% of TIR3B, 50–80% of TIR4 and 95–99% of TIR5 are tumor, as assessed only upon thyroidectomy. Although it has been well established that lncRNAs (long non-coding RNA transcripts) play a fundamental role in cancer biology, knowledge about the specific role of these transcripts in the initiation and progression of DTC is still poorly understood.
Aim
The aim of this study is to identify a molecular profile based on lncRNAs expression that may discriminate between benign and malignant nodules.
Methods
A cohort of 50 patients, male to female ratio 1:5 was enrolled at the Endocrinology and Metabolism Diseases Unit, Fondazione Policlinico Gemelli, Rome Italy. Inclusion criteria: thyroid nodules more than 1 cm with suspicious ultrasound characteristics. Gene expression analysis was performed using Droplet Digital PCR (ddPCR) on the following biological samples: i) cells from Fine Needle Aspiration (FNA) biopsy, ii) residual cell samples from FNA prepared for cytology (FNA-ThP) and iii) fresh thyroid tissue explanted after surgery.
Results
A panel of transcripts were first analyzed by ddPCR on fresh DTC tissue: the three thyroid-specific genes (TG, TPO and NIS), six cancer-associated lncRNAs (MALAT1, NEAT1, HOTAIR, H19, PVT1, MEG3) and two housekeeping genes (GAPDH and P0). According to their higher expression in DTC, TG and MALAT1 were selected as markers for thyroid specificity and malignant phenotype, respectively. Next, gene expression by ddPCR was analyzed in both FNA and FNA-ThP samples after RNA extraction (Single Cells Shot, Biorad), reverse transcription (High Capacity kit, Applied Biosystems) and preAmp step (EvaGreen Master Mix, Biorad). As preliminary results, 6 out 14 patients (12 TIR2 and 2 TIR3) appear to express MALAT1 20-200 fold higher that TG or P0, with the following distribution: 2/2 TIR3 patients and 4/12 TIR2. Of note, 2/4 TIR2 were large thyroid nodules (3–4 cm).
Conclusion
In conclusion, characterization of selected lncRNAs in Fine Needle Aspiration biopsies may represent a novel diagnostic approach potentially contributing to take the final decision to proceed or not with surgery.

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GP242

New markers of follicular thyroid cancer found with wide-panel next-generation sequencing

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Introduction
Thyroid nodules may be detected in up to 67% of the adult population and constitute big diagnostic challenge. Presurgical differentiation of follicular lesions between follicular adenoma (FA) and follicular thyroid carcinoma (FTC) is particularly difficult. Commercially available gene panels cover only a few, selected mutations to help in discrimination between FA and FTC. The aim of this study was to comprehensively assess the genetic background of thyroid follicular lesions and to find genetic alterations that are present solely in FTC and therefore may serve as malignancy determinants.
Material and methods
The material from 50 consecutive formalin-fixed, paraffin-embedded (FFPE) FA and FTC specimens were re-reviewed to confirm the diagnosis and to indicate the most appropriate part of the specimen for DNA sample collection. DNA was acquired from FFPE. The NGS sequencing on *Ion PGM Sequencer* (*Thermo Fisher*, USA) employing *Ion AmpliSeq Cancer Hotspot Panel v2* was conducted. The obtained data from genomic experiments were subjected for analysis using dedicated software and compared with clinical data. In case when no alterations using *Cancer Hotspot Panel* was identified, an *Ion AmpliSeq Comprehensive Cancer Panel* was employed.
Results
The sequencing has revealed various mutations present only in case of FTC (but not in FA), which may serve as potential markers of malignancy of a follicular lesion, such as: *APC, CTNNB1, EGFR, FBXW7, HBF1A, HNF1A, KRAS, NRAS, PIK3CA, TP53.* The most common mutation was *TP53.* In the specimens of FA, *JAK3, NOTCH1* and *PDGFRA* mutations were found. *BRAF, KIT, PTEN* and *SMARCB1* were found in both FA and FTC, although were much more common

in the latter. After extension of the gene panel to *Comprehensive Cancer Panel* we found that *ARID1A, BLNK, MSH2* and *SYNE1* were present only in FA, with the most frequent occurrence of BLNK mutation.
Conclusions
The results of our study demonstrate that FA and FTC may differ with detectable genetic alterations, which may support advanced follicular lesions diagnostics. Using wide gene panel including various mutations previously reported in different malignancies might be a good strategy to differentiate follicular thyroid lesions both preoperatively (to decide on therapy) and postoperatively (to confirm diagnosis in doubtful cases). Finding of new genes possibly participating in FTC pathways may enable searching for novel targeted therapeutic methods.

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GP243

Prognostic value of N0 classification in differentiated thyroid cancer

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Introduction
The TNM classification of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is the most widely used thyroid cancer staging system. The 8th edition was published in 2016 and introduced modifications to the N0 classification. Histological analysis is no longer necessary for patients to be classified as N0, as long as there is no evidence of lymph node (LN) metastasis in the preoperative imaging tests or clinical evaluation. Therefore, patients may be classified as N0a (without cytological or histological evidence of LN metastasis) or N0b (without clinical or radiological evidence of LN metastasis). Our study aimed to evaluate and compare the prognosis of patients with differentiated thyroid carcinoma (DTC), classified as N0a or N0b.
Methods/design
This was a retrospective study of 594 patients identified from our institutional database, who underwent surgery for DTC between 2000 and 2014. All patients had: apparently complete tumour resection, absence of LN or distant metastasis at diagnosis and non-aggressive histological variant. The association between variables was evaluated using Shi-square and Student's *T*-tests.
Results
All patients were followed for a minimum of 3 years postoperatively (146.3 $\pm$ 92 months). The majority of patients were female (88%) and had papillary thyroid carcinoma (89%). Three hundred and forty six patients (58.2%) were classified as N0b and the remainder as N0a (41.8%). Mean age was similar in both groups (51.3 years in the N0a group and 50.4 years in the N1b group, $P=0.303$). There were no significant differences between N0 classification and tumor size (mean size 16.4 mm vs 18.4 mm, $P=0.135$), multifocality (24.4% vs 26.3%, $P=0.214$), extra-thyroid extension (16.7% in both cases, $P=0.738$), treatment with radioactive iodine (44% vs 51.4%, $P=0.1$), persistence of disease (1.3% vs 2.9%, $P=0.415$), recurrence of disease (0.8% vs 0.9%, $P=0.99$) and disease-specific mortality (0.4% vs 0.3%, $P=0.962$).
Conclusion
Our results suggest that there is no difference in outcome of patients classified as N0a or N0b, regarding disease specific mortality, recurrence and persistence of disease. Therefore, preoperative clinical and imaging evaluation of the cervical region should play a major role in the staging of DTC patients.

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GP244

Implementation of the British Thyroid Association thyroid nodule classification: a general UK hospital perspective

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Introduction
In 2014, the British Thyroid Association (BTA) issued guidance on thyroid cancer and introduced a new scoring system for thyroid nodules based on their sonographic appearances (U1-U5). The guidelines specified that nodules with indeterminate or suspicious appearances (U3-U5) should undergo fine needle aspiration (FNA) assessment. This study audits the implementation of the guidelines in our hospital and evaluates any changes in the management of thyroid nodules.
Patients and methods
A list of all the patients undergoing thyroid ultrasound at Chelsea and Westminster Hospital over a 1-year period from January 2016 to December 2016 was obtained. A reference cohort of thyroid ultrasounds performed before the publication of the guidelines (July 2013 to June 2014) was also obtained from the electronic data base. Patients with no nodules and patients aged $<$ 18 years were excluded. The electronic records were used to collect data regarding U classification, FNA cytology, surgery and histopathology results for both groups.
Results
A total of 793 patients were identified: 352 in the pre-guidelines cohort and 441 in the post-guidelines cohort. Patients were matched for age (52 $\pm$ 15.8 and 52 $\pm$ 16.3 respectively) and gender (1 male: 9 female ratio, in both groups). There was 70% compliance in reporting U grading as per the classification system. Pre-guidelines, 35% (95% CI 0.29–0.42) of patients had an FNA compared to 22% (95% CI 0.18–0.27) post-guidelines ($P < 0.05$). Pre-guidelines, 9% (95% CI 0.06–0.12) of patients underwent surgery compared to 10% (95% CI 0.07–0.13) post guidelines ($P=0.64$). Thyroid cancer was confirmed in 2% (95% CI 0.09–0.48) of the cases pre-guidelines and in 1.9% (95% CI 0.08–0.38) of the cases post-guidelines ($P=0.86$).
Conclusions
Our results have demonstrated a reduction in the number of patients being subjected to FNA with no reduction in the number of surgeries or cancer detection. There were initial challenges in adherence to reporting a U classification and a number of interventions were implemented to increase this.

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GP245

Dynamic risk stratification in the follow-up of children and adolescents with differentiated thyroid cancer

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Context
Risk stratification for persistent disease is an important step in pediatric differentiated thyroid cancer (DTC) management. The dynamic risk stratification (DRS) is a well validated system for adults, but not yet for children and adolescents.
Objective
To evaluate DRS performance and other prognostic factors in pediatric DTC.
Design
Cohort study.
Setting
Four DTC referral centers at tertiary teaching hospitals.
Patients
Patients aged $\leq$ 18 years at the time of DTC diagnosis.
Main outcome measures
All patients were classified according to risk stratification system of the 2015 ATA Children DTC guidelines. Patients were also classified according to DRS (excellent, indeterminate, biochemical, or structural incomplete responses). Disease status was evaluated after initial therapy and at last follow-up.
Results
Sixty-six patients were studied: 54 (81.8%) girls, age 14.5 $\pm$ 3.0 years, 62(93.9%) papillary thyroid carcinomas. Tumor size was 2.3 cm (P25-75,1.6-3.5), and 41 (63.1%) had cervical and 18 (27.7%) distant metastasis at diagnosis. All patients underwent total thyroidectomy and 63 (95.5%) received radioiodine. Patients were classified according to DRS after initial therapy ($n=63$) as follows: 21 (33%) excellent, 13 (21%) indeterminate, 6 (9%) biochemical, and 23 (37%) structural incomplete responses. Notably, after 6.0 years (P25-75,2.7-10.0), most

patients remained in the same category. Prognostic factors associated with persistent disease in the univariate analysis were TNM, ATA risk, DRS and stimulated postoperative thyroglobulin (sPOTg). Interestingly, the sPOTg cutoff of 37.8 ng/mL displayed 81% sensitivity and 100% specificity to predict excellent response.

Conclusion

DRS after initial therapy and sPOTg are strong predictors of disease status and might be helpful on defining follow-up strategies in pediatric DTC.

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Thyroid Non Cancer

GP246

Genistein Increase Thyroid Hormone and 7 alpha-hydroxycholesterol concentrations in the liver of middle-aged male rats

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Obesity, a major public health problem, is associated with hypercholesterolemia and other metabolic disorders, which are potent risk factors for athero-thrombotic disease, a leading cause of mortality worldwide. Advances in both dietary and pharmacological interventions contribute significantly to prevention and treatment of modifiable risk factors. Consumption of purified soybean isoflavones was reported to reduce plasma and liver cholesterol levels. The precise mechanism has not been established, but it has been suggested that these effects occur through an increase in bile acid excretion. The initial and rate limiting step in the classical pathway of hepatic synthesis of bile acids from cholesterol is the enzymatic addition of a 7α hydroxyl group by cholesterol 7α-hydroxylase forming 7α-hydroxycholesterol. Thyroid hormones have been shown to up-regulate expression of this enzyme. We previously reported that subcutaneously administered genistein impaired thyroid functioning in middle-aged rats, but at the same time increased expression of T3-activated genes and increased deiodinase type 1 enzyme activity in the liver. In this study we aimed to further determine effects of genistein on concentrations of thyroid hormones, total cholesterol and 7α-Hydroxycholesterol in the liver. Thirteen-month-old male Wistar rats were injected subcutaneously with 35 mg/kg of genistein, while controls received vehicle alone daily during 4 weeks. For determination of iodothyronines liquid chromatography-mass spectrometry was applied, while total cholesterol and 7α-hydroxycholesterol were determined by gas chromatography/mass spectrometry. Our study results clearly demonstrate that genistein increased ($P<0.05$) concentration of T4 and T3 in the liver of middle-aged male rats. In line with this, concentration of 7α-hydroxycholesterol also increased ($P<0.05$), but the total cholesterol levels remained unchanged. In conclusion, genistein increased hepatic availability of thyroid hormones, in accordance with detected increase in 7α-hydroxycholesterol level in the liver. The obtained data brought new light on the mechanisms involved in biological processes in the liver induced by genistein.

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GP247

Serum FT4 levels predict incidence of type 2 diabetes and cardiovascular disease in the general population

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Background

Skin autofluorescence (SAF), measured with the AGE-reader, predicts cardiovascular disease (CVD) and type 2 diabetes (T2D). Thyroid hormone levels (TH) may affect this association. In the present study, we examined whether TH predict 4-years risk of T2D, CVD and mortality in the general population independently of SAF.

Methods

We included 28245 participants (age 44 ± 12 years, BMI 25.9 ± 4.3 kg/m^2) of the Dutch Lifelines Cohort Study, who had SAF and TH (TSH, FT4, FT3, Roche Modular E170 Analyzer) measured, and were not known to have diabetes or CVD at baseline, or using medication influencing TH (including levothyroxine). Diagnosis of incident T2D was by self-report, or fasting blood glucose ≥ 7.0 mmol/l or HbA1c ≥ 6.5% at follow-up; diagnosis of incident CVD was by self-report. Metabolic syndrome (MetS) was defined by NCEP-ATPIII criteria. Mortality was ascertained with the Municipal Personal Records Database. The influence of TH on the composite outcome of incident T2D, CVD and mortality, and these outcomes separately, was evaluated with logistic regression.

Results

After a median follow-up of 4 (range 1–9) years, 325 participants had died, 415 developed CVD, and 377 developed T2D. For the composite outcome, TH were identical in cases vs. non-cases. Subjects with incident T2D were significantly older (54 vs 44 years), had lower FT4 compared to no-diabetes (15.2 ± 2.1 vs 15.6 ± 2.1 pmol/l, $P<0.0001$), but similar FT3 and TSH, while those with new-onset CVD were older (57 vs 44 years) and had borderline significantly higher FT4 levels (15.9 ± 2.1 vs 15.7 ± 2.2, $P=0.06$). Logistic regression showed that each 1.0 pmol/l lower level of FT4 was associated with an 11% higher T2D risk, adjusted for SAF, age and gender. After further adjustment for presence of MetS, glucose and/or HbA1c, FT4 retained its significance (OR 0.92, $P=0.006$). In contrast, each 1.0 pmol/l higher FT4 was associated with a 5% increased CVD risk ($P=0.02$), adjusted for SAF, age and gender but this association lost its significance when adjusting further for blood pressure and cholesterol. In the multivariate models, higher FT3 was associated with increased T2D and CVD risk; there was no association between TSH and outcome.

Conclusions/interpretations

Serum FT4 levels have opposite effects on risk of development of T2D and CVD in the general population, independent of SAF, and presence of metabolic syndrome. Next steps will be to elucidate underlying mechanism(s).

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GP248

Thyroid function in early-treated adult PKU patients

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Introduction

Phenylketonuria (PKU) is a rare inherited metabolic disorder that leads to the toxic accumulation of phenylalanine (Phe) causing usually severe mental retardation and seizures. The basis of the lifelong therapy is low in natural-protein diet and Phe-free amino acid mixtures, that provide the daily necessary amino acids, vitamins and micronutrients, such as Iodine and Selenium. It is not well known, whether the adherence to the therapy can influence the thyroid function in early-treated adult PKU patients.

Method

A prospective, cross-sectional study was conducted to assess the thyroid function, ultrasound structure and Iodine status of early-treated adult PKU patients. Seventy-five PKU patients (age 18–41 years) were included in this study. Based on their blood Phe values they were divided into two groups, with the cut-off point being the upper limit of 600 μmol/l: on-diet ($n=27$) and loose-diet ($n=48$) group. Spot urine Iodine concentration (I) and Iodine/creatinine ratio (I/Cr), blood Phe, Tyr, free triiodothyronine (fT3), free thyroxine (fT4), fT3/fT4 ratio, thyroid-stimulating hormone (TSH), thyroglobulin, anti-thyroglobulin antibody, anti-thyroid peroxidase antibody were measured and thyroid ultrasound was performed. The results were compared between the two groups.

Results

None of the PKU patients have abnormal thyroid function. The prevalence of thyroid nodes seen on ultrasound was 21.3%. Blood Phe or Tyr even Phe/Tyr ratio were not associated with TSH, fT4, fT3 or fT3/fT4 ratio or with the antibodies. However, we observed a significant difference in the urine Iodine concentration

and I/Cr ratio between the two groups ($P<0.05$, $P<0.01$ respectively). The loose-diet group based on the I concentration (median of 99.14 μg/l, 28.8% <50 μg/l, 51.1% <100 μg/l) could be classified as Iodine deficient sub-population. Blood Phe correlated inverse with the I concentration and I/Cr ratio ($r=-0.28$, $P<0.05$; $r=-0.37$, $P<0.01$), while blood Tyr showed correlation with I/Cr ($r=0.30$, $P<0.05$). fT3, TSH, Thyroglobulin, thyroid antibodies and fT3/fT4 ratio showed no significant difference between the groups, however, fT4 was significantly higher in the on-diet group ($P<0.05$, on-diet: 14.15 pmol/l ± 1.9 S.D.; loose-diet: 13.23 pmol/l ± 1.3 S.D.).

Conclusion

The result of this study suggests that Iodine status is influenced by the adherence to therapy in early-treated adult PKU patients. However, thyroid function might not be affected in adult PKU.

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P249

Abnormal thyroid enzymes in critically ill patients with no known prior thyroid disorder are an independent predictor of mortality

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Background

Sick euthyroid syndrome is a well-known condition and no additional treatment is often required. However various authors have postulated that there is an effect of abnormal thyroid function on the outcomes of hospitalized patients. In our study, we chose to study the effect of thyroid function abnormalities and their independent effect on mortality of critically ill patients who had no known prior thyroid diseases.

Methods

Data was obtained from 'Medical Information Mart for Intensive Care III' database between 2001 and 2012. All patients whose Thyroid Stimulating hormone (TSH) and Thyroxine (T4) were tested were considered. Patients who had prior thyroid diseases were removed. The rest were split into multiple groups based on their TSH and T4 levels during their ICU stay. The groups are outlined in Table 1. Base outcome group was those with normal TSH and normal T4 (Group Zero - G0). Multinomial logistic regression with length of stay (LOS) and Simplified Acute Physiology Score (SAPS) II as co-variables were run to assess the Relative Risk Ratios (RRR) of 30-day mortality with altered TSH and T4 levels.

Table 1 RRR of 30-day mortality of patients admitted to critical care units compared to those with normal thyroid values (adjusted for SAPS II and LOS).

Group	T4	TSH	RRR	*P* value	95% Conf Interval
G0	Normal	Normal		Reference	
G1	Low	Low	3.8	0.021	(1.2–11.7)
G2	Low	Normal	2.1	0.031	(1.1–4.2)
G3	Low	High	2.1	0.002	(1.3–3.3)
G4	Normal	Low	1.2	0.314	(0.8–1.89)
G5	Normal	High	1.4	0.018	(1.1–1.9)
G6	High	Low	0.9	0.849	(0.4–1.9)
G7	High	Normal	1.7	0.040	(1.02–2.8)
G8	High	High	3.7	0.001	(1.7–7.7)

Results

Total of 2970 adult ICU admissions who had no underlying thyroid disease were considered for the study. Among them, two groups, G1 (High TSH and High T4) and G8 (Low TSH and Low T4) when compared to the base outcome had a significantly increased RRR of mortality. The RRR for 30-day mortality, among G1 compared to G0 was 3.79 ($P=0.021$) and 3.67 ($P=0.001$) in G8 compared to G0.

Conclusion

Among the critically ill patients and specifically for those without prior thyroid illness, we postulate that T4 and TSH can be used as independent predictors of mortality. When both the values are altered, it might signify a more profound metabolic derangement, needing specific attention, as compared to the traditional subclinical hypo and hyperthyroidism.

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GP250

Assessment of carotid intima-media thickness and endothelial dysfunction in patients with hypothyroidism

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Introduction

Hypothyroidism is associated with increased risk of atherosclerosis. We assessed both carotid intima media thickness (CIMT), as a marker of atherosclerosis, and endothelial dysfunction in patients with hypothyroidism.

Methods

We included 70 female patients with hypothyroidism (age 18–55 years), 40 patients with overt and 30 patients with subclinical hypothyroidism (SCH). Forty age and sex matched subjects with normal thyroid functions were also included as a control group. CIMT was measured using high-resolution colour-coded Doppler ultrasonography. Endothelial function was assessed by measuring the percent of change in blood flow following heat mediated vasodilation using Laser Doppler flowmetry.

Results

CIMT was significantly higher in patients with overt and subclinical hypothyroidism as compared with the control group (0.7 + 0.2 and 0.6 + 0.2 mm respectively vs 0.45 + 0.07 mm, $P<0.001$ for both). The percent of change in blood flow following heat mediated vasodilation was significantly impaired in patients with overt and subclinical hypothyroidism as compared with the control group (327.5 + 17 and 545 + 406% respectively vs 897.7 + 195.4%, $P<0.001$ for both). The impairment was more significant in patients with overt hypothyroidism as compared with those with SCH ($P=0.014$). There was a significant negative correlation between CIMT and the percent of change in blood flow following heat mediated vasodilation in patients with overt and subclinical hypothyroidism ($P<0.001$ for both).

Conclusion

CIMT, as a marker of atherosclerosis, is significantly higher in patients with overt and subclinical hypothyroidism compared with normal control subjects. Impairment of endothelial function is a contributing factor to the increased risk of atherosclerosis in both groups of patients.

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GP251

Thyroid-specific mitochondrial dysfunction results in abnormal thyrotropin responses

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Background

Optimal production of cellular energy and metabolites in mitochondria is one of the most important factors in endocrine organs that accomplish the momentary adaptation to ligand stimulation, such as insulin secretion and aldosterone biosynthesis. Although it has been suggested that thyroid gland function is also largely dependent on mitochondrial function, functional behavior of thyroid gland on compromised mitochondrial function remained to be identified. In this study, we have developed the new animal model of thyroid-specific mitochondrial dysfunction using standard gene targeting technology to understand the role of mitochondria OxPhos dysfunction in thyroid gland.

Methods

We have analyzed the histological and functional phenotypes of the mice which has thyroid specific mitochondrial dysfunction by targeting *Crif1* gene which is involved in intramitochondrial production of OxPhos complex subunits.

Results

We analyzed the phenotypes of the mice with mitochondrial OxPhos deficiency. Homozygote thyroid-specific mitochondrial dysfunction (ThyCKO) mice retarded growth and died prematurely in PN21 to 35 days with severe thyroid dysfunction. Histology of homozygote ThyCKO mice showed distortion of thyroid follicles and oncocytic change of cells. Serum TSH and thyroid hormone levels showed no difference between 10 week old wild type and heterozygote

ThyCKO mice. Unexpectedly, TSH injections (6 μg/day) to 10 week old heterozygote ThyCKO mice exacerbated ER swelling combined with destruction of mitochondrial cristae structure, resulting in lower secretion of thyroid hormone.
Conclusion
This study suggested that mitochondrial OxPhos defect may cause structural and functional changes of thyrocyte which may lead the progressive chronic nonautoimmune failure of thyroid gland.

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GP252

T3 enhances GLUT2, PEPT1 and CD36/SR-B2 content in the intestinal epithelium of mice

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Introduction and aim
Thyroid hormones (THs) regulates metabolism in adults, such as controlling energy balance by regulating energy expenditure and its storage. Hyperthyroidism increases thermogenesis, which results in the increase of the metabolic rate. THs, when combined with their receptor, can induce the expression of some genes, which can reflect on the content and activity of specific proteins. There are studies showing that THs affect the uptake of nutrients, such as glucose and peptides, but it is not well known how it works. Therefore, the current study has the aim to evaluate the impact of hypo and hyperthyroidism in the nutrients transporters content, such as carbohydrate, peptides and lipids transporters in the intestinal epithelium.
Materials and methods
In this study, mice C57BL/6, male and adults were distributed in three groups: control (vehicle/saline), hypothyroid (Propylthiouracil - PTU) and hyperthyroid (Triiodo-L-thyronine - T3). The animals were injected with saline, PTU (12.5 mg/Kg) or (T3 0.25 μg/g) for 30 days. At the end of the treatment, the mice were killed and the intestinal epithelium was removed to evaluate the transporters of carbohydrates (SGLT1, GLUT2 e GLUT5), protein hydrolysate (PEPT1) and lipids (NPC1L1, CD36/SR-B2 e FATP4) by Western blotting technique. Since NHE3 plays an important role in the sodium and peptides absorption, it was evaluated as well.
Results
Hyperthyroidism increased the GLUT2, CD36/SR-B2 and PEPT1content when compared to the control mice. SGLT1, GLUT5, FATP4 and NPC1L1 remained unchanged after T3 treatment. T3 induced a little increase of NHE3, but not statistically yet. The hypothyroidism did not affect the nutrients transporters nor NHE3 compared to the control group.
Conclusion
Since THs increase the glucose uptake by intestine through sodium independent mechanism, which is well-established, the increased GLUT2 in the intestine after T3 treatment could explain how THs stimulate glucose absorption. Furthermore, T3 also increased PEPT1 and CD36/SR-B2 content, which could be a physiological mechanism to provide nutrients (glucose, amino acids and fatty acids) and sustain the high metabolic demand and thermogenesis, which are common findings in the hyperthyroidism condition.

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GP253

Identification of new thyroid hormone dependent biomarkers for a successful replacement therapy

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Thyroid hormones (TH) play a pivotal role in embryonal and postnatal development in vertebrates, hence, their secretion is highly regulated. In clinical practice TSH and free T4 (fT4) are commonly used as the most reliable parameters to evaluate the TH status. But they only represent the TH receptor β driven status of the hypothalamic-pituitary-thyroid axis while organ or tissue specific TH availability may be different. This discrepancy originates in the tissue specific unequal distribution of proteins modulating local T3 signalling like TH transporters, deiodinases and TH receptors (TRα and TRβ). To identify patients with tissue specific hypo – or hyperthyroidism, new biomarkers are urgently needed. By comparing studies of experimental thyrotoxicosis in human and mouse using OMICs techniques, we discovered 16 serum proteins concordantly regulated in both species, which are predominantly expressed in liver, lymphoid system or extracellular matrix. To validate these putative targets, we conducted a follow-up mouse study with a Methimazol and sodium perchlorate induced hypothyroid group and a T3 or T4 induced hyperthyroid group. Subsequent qPCR analysis revealed gene expression changes of our candidates under hypo – and/or hyperthyroid conditions in liver, bone and spleen. To characterise these putative biomarkers in greater detail, we aimed to determine the secreting cell types and validate their T3-dependence in different model systems. We therefore investigated target gene expression of the human hepatocyte cell line HepG2, primary murine osteoclast, -blasts and isolated murine B-cells, T-cells and monocytes under either eu-, hypo- or hyperthyroid conditions or with a mutation in either TRα or TRβ or both. Among these candidates the expression of the macrophage derived protein, CD5L, was highly T3-dependent in liver, spleen and bone. CD5L is thus regarded as the most promising putative TH – biomarker to be further investigated under pathophysiological clinical conditions.

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GP254

Proteome analysis of 3,5-T2-treated primary mouse hepatocytes

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Introduction
Besides the classical thyroid hormones T4 and T3 the endogenous thyroid hormone metabolite 3,5-diiodothyronine (3,5-T2) attracted attention during the last years due to its metabolic activity. 3,5-T2 exerts thyromimetic action on the hypothalamus-pituitary-thyroid axis and the heart as well as on energy and lipid metabolism. In previous liver transcriptome analyses of 3,5-T2-treated lean and diet-induced obese male mice, effects on hepatic lipid, steroid, xenobiotic, and thyroid hormone metabolism were observed.
Objectives
Applying an untargeted mass spectrometry based proteome analysis approach for 3,5-T2-treated primary mouse hepatocytes, we intended to confirm previous *in vivo* transcriptome data and to identify novel protein targets and pathways of hepatic 3,5-T2 action.
Materials & methods
Primary hepatocytes isolated from male mouse liver were cultivated under FCS-free conditions and treated with 100 nM 3,5-T2 for either 6, 24, 48 or 72 h ($n = 3$ per group). Proteins were prepared and digested using Trizol and FASP (filter-aided sample preparation), respectively. Proteomes were analyzed using LC-MS/MS measurement and data analysis was performed *via* MaxQuant and GeneData Analyst software. Pathway analysis of proteins exhibiting significantly altered amounts was carried out using the Ingenuity Pathway Analysis (IPA) software.
Results
The proteomics approach revealed 852 proteins exhibiting significantly altered amounts in 3,5-T2-treated primary hepatocytes compared to their time matched controls ($P \leq 0.05$, fold change $\geq |1.5|$). Notably, the highest number of proteins with significantly changed amounts was observed after 48 h of treatment, while after 6 and 24 h 4.5-times less proteins were altered. The greatest overlap of 92 proteins was observed between the time points 24 and 48 h of 3,5-T2 treatment. As identified by IPA, proteins showing significant alterations mainly belong to the pathways 'EIF2 signaling', 'regulation of eIF4 and p70S6K signaling', 'mTOR signaling', various degradation pathways for intermediary metabolites, as well as proteins involved in steroid hormone metabolism.
Conclusion
The untargeted mass spectrometry approach identified a variety of proteins and pathways altered by 3,5-T2 treatment in primary mouse hepatocytes as well as the confirmation of previously indicated 3,5-T2 effects on mouse liver transcriptomes and functional readouts. To further extend our knowledge of 3,5-T2 action, a transcriptome analysis of the current study is planned to create a complementary dataset.

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Thyroid Non Cancer - Autoimmune Thyroid Disease/Pregnancy

GP255

MicroRNA-4443 causes CD4+T cells dysfunction by targeting TRAF4 in Graves' disease

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Context
Aberrant CD4+T cell function plays a critical role in the process of Graves' disease (GD). MicroRNAs (miRNAs) are important regulators of T cell activation, proliferation and cytokine production. However, the contribution of miRNAs to CD4+T cell dysfunction in GD remains unclear.
Objective
To investigate how certain miRNA causes aberrant CD4+T cell function in GD patients.
Methods
We compared the expression pattern of miRNAs in CD4+T cells from untreated GD patients with those from healthy controls. The most significantly dysregulated miRNAs were selected and their correlations with clinical parameters were analyzed. The effect of miR-4443 on CD4+T cells cytokines production and proliferation was assessed. The potential gene target was identified and validated.
Results
GD patients had unique pattern of miRNA expression profile in CD4+T cells comparing to healthy subjects. MiR-10a, miR-125b and miR-4443 were the three most significantly dysregulated miRNAs. The elevated miR-4443 levels were strongly correlated with clinical parameters in an independent dataset of untreated GD patients (N=40) while miR-4443 was normally expressed in GD patients with euthyroidism and negative TRAb level. We found that miR-4443 directly inhibited TNFR-associated factor (TRAF) 4 expression to increase CD4+T cells cytokines secretion as well as proliferation through the NF-κB pathway. Furthermore, the TRAF4 levels in GD patients were inversely correlated with miR-4443, and knocking down TRAF4 had a similar effect with miR-4443 overexpression.
Conclusion
The increased expression of miR-4443 induced CD4+T cells dysfunction by targeting TRAF4, which may cause Graves' diseases.

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GP256

Are Thyrotropin Receptor Antibodies (TRAb) being used to diagnose the aetiology of hyperthyroidism?

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Introduction
Hyperthyroidism is a prevalent condition which affects approximately 2% of the female population and 0.2% of the male population in the UK. 75% of cases are caused by the auto-immune condition, Graves' disease. Thyrotropin receptor antibodies (TRAb) are raised in 90% of patients with Graves' disease and are commonly used to investigate the aetiology of thyrotoxicosis.
Background
TRAb can be used to confirm Graves' disease due to its high sensitivity and specificity, at 98 and 99% respectively. The National Institute for Health and Care Excellence (NICE) clinical advice is to test for TRAb in patients with confirmed hyperthyroidism. Patients who have negative antibodies should then undergo radionuclide thyroid uptake scans.
Aim
To see if patients who attended the endocrinology outpatient clinic at the Royal Liverpool University Hospital had TRAb tested, and to compare this to other methods of investigating the aetiology of hyperthyroidism.
Method
The records of 150 patients who attended the endocrinology outpatient clinic from 2003 to 2017 were analysed. Data was collected to assess if they had TRAb tested. This data was compared to the number of patients who had thyroid peroxidase (TPO) antibody tested, and whether radionuclide thyroid uptake scans were performed.
Results
In the sample of patients, aetiologies of thyrotoxicosis included Graves' disease (107), toxic multi-nodular goitre (33), solitary toxic nodule (1), thyroiditis (6) and non-specified hyperthyroidism (3). 95.33% of these patients had TRAb tested, 81.33% had TPO tested and 63.33% had a thyroid uptake scan. Of the patients who had Graves' disease, 57% of patients had a thyroid uptake scan despite having a positive TRAb assay.
Conclusion
From this audit it can be confirmed that most of the patients with hyperthyroidism, who attended the endocrinology outpatient clinic, had their TRAb tested. However, it has been shown that there is an overuse of thyroid uptake scans in patients with Graves' disease who had a positive TRAb assay. This demonstrates that in clinical practice there is a lack of continuity between interpreting TRAb results and ordering uptake scans. By only performing the scans in TRAb negative patients, clinicians can provide a more clinically efficient and cost-effective service.

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GP257

Impact of TSH during the first trimester of pregnancy in obstetric and fetal complications: Usefulness of 2.5 mIU/l cut-off value

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Background
An association of pregnancy outcomes with subclinical hypothyroidism have been reported, however, there still exists a strong controversy regarding whether subclinical hypothyroidism ought to be dealt with or not. The latest American Thyroid Association's guideline gives support to a higher TSH upper reference range of 4 mIU/l than the one proposed a few years ago of 2.5 mIU/l for the first trimester of pregnancy, in the absence of local normal ranges of TSH. In spite of this, the controversy regarding the upper limit of TSH during pregnancy for the treatment of subclinical gestational hypothyroidism seems to be far from being clarified.
Objective
To evaluate the association of fetal-maternal complications with first trimester maternal TSH values.
Patients and methods
A retrospective study in a single tertiary care hospital was performed. Thyrotropin (TSH) universal screening was performed between weeks 9–12 of gestation in 1981 pregnant women during 2012. Outcomes included fetal-maternal complications and newborn health parameters.
Results
Median TSH was 1.72 (0.99–2.61) mIU/l. The incidence of perinatal loss, miscarriage and stillbirth was 7.2, 5.9 and 1.1% respectively. Median TSH of women with and without miscarriage was 1.97 (1.29–3.28) vs 1.71 (0.96–2.58) mIU/l ($P=0.009$). Incidence of preeclampsia was 3.2%; TSH in these women was 2.10 (1.40–2.74) vs 1.71 (0.98–2.59) mIU/l in those without ($P=0.027$). TSH in women with dystocia in labor was 1.76 (1.00–2.53) vs 1.68 (0.94–2.59) mIU/l and in those who gave birth with normal progression ($P=0.044$). Women with TSH 2.5–5.1 mIU/l had a higher risk of perinatal loss (OR 1.589 (1.085–2.329), $P=0.017$), miscarriage (OR 1.702 (1.126–2.572), $P=0.012$) and premature birth (OR 1.379 (1.013–1.876), $P=0.041$). There was no association with the other outcomes analyzed. A composite variable was constructed including fetal-maternal complications and newborn health parameters in order to assess which TSH value would predict an adverse outcome by using ROC curves. The area under the curve obtained was 0.528, not allowing the definition of a useful cut-off point predicting adverse outcomes.
Conclusions
Our data support that higher levels of TSH within the reference normal concentrations during the first trimester are associated with higher risk of adverse

obstetric outcomes (perinatal loss, miscarriage and premature birth). In our study, there is not a useful crude TSH cut-off point predicting adverse outcomes.

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GP258

Influence of levothyroxine treatment in pregnant women with thyroid antiperoxidase antibodies

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Introduction
Thyroid antiperoxidase antibodies above the cut-off value (ATPO +) may increase the risk of maternal-foetal complications and could modify the treatment criteria. The aim of the study is to consider the impact of levothyroxine administration on maternal-foetal complications in ATPO+ pregnant women with delivery in 2016.
Methods
In Leon's health area (Spain), universal screening for gestational thyroid dysfunction is performed. ATPO + was ≥35 U/ml (Immulite 2,000). The cut-off for subclinical gestational hypothyroidism (HSG) was TSH >3.72 mU/l (Roche kit) The maternal-foetal variables studied were gestational age, birth weight and type of delivery:
-Preterm birth is considered when pregnancy's completed before week 37.
- Low birth weight is considered <2500 gr.
The qualitative variables were expressed by absolute numbers and percentages, and the quantitative variables in mean and standard deviation. The X2 test was used to evaluate differences between proportions and T student test to compare means. The association among risk factors and treatment was studied by relative risk and confidence interval.
Results
We analysed 1980 deliveries, 22 miscarriages and 18 deliveries outside our hospital. 87 were eliminated by previous treatment with thyroxine. Of 1672 screenings: 142 (8.50%) had ATPO +, 286 (17.11%) HSG and in 55 (3.29%) HSG and ATPO+ coexist. We studied 131 ATPO+ pregnant women: 45% ($n=59$) of patients received treatment during pregnancy. Of those who received treatment during pregnancy, presented preterm delivery 3.39% vs 11.11% that didn't receive thyroxine (RR: 0.31, 95% CI: 0.07–1.40). The mean gestational age of the newborns was 39.05 (1.53) weeks, for patients treated with levothyroxine, it increases up to 39.15 (1.4) weeks, slightly higher than those who didn't receive treatment ((38.97 (1.64) ($P=0.50$)). We found 6.78% children with weight <2500 gr in patients with treatment and 5.56% in those who weren't treated ($P=1.00$). 15 untreated women (20.83%) underwent a caesarean section and 10 treated pregnant women (16.95%) ended their pregnancy as a caesarean section ($P=0.84$). The average dose of thyroxine was 71.53 µg/day (0.95 µg/kg per day). With this dose, the average TSH at the end was 1.76 mU / l.
Conclusion
According to these results, there is neither positive or negative impact of the administration of levothyroxine to pregnant women ATPO +. There may be a protective tendency on preterm delivery, although larger studies are needed.

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GP259

Thyroid disorders in patients with advanced neoplastic disease treated with immune checkpoints inhibitors

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The use of immune checkpoint inhibitors (ICPI) for treatment of different advanced cancers has opened a new therapeutic window. Thyroid dysfunction is an often side effect described for these drugs.
Objectives
To describe the thyroid alterations found in oncologic patients undergoing treatment with ICPI.
Materials and methods
A descriptive, retrospective study of oncologic patients receiving treatment with ICPI referred to the Endocrinology Clinic of our Center for thyroid disorders from October 2013 to January 2018.
Results
Thirty-four patients were detected, mean age 59.9 years old (from 34 to 79), 64.7% were women. Neoplasm treated were mainly breast (17.6%), lung (17.6%) and melanoma (14.7%), among others. The immunotherapy received was in monotherapy regimen in the majority of cases (73.5%), using a combination of ICPI in the remaining cases (Pembrolizumab 35.3%, Atezolizumab 20.6%, Nivolumab + Ipilimumab 14.7%, Nivolumab 11.8%, Nivolumab + Anti-LAG3 8.8%, Tremelimumab + Durvalumab 2.9%, Tremelimumab 2.9%, PDR001 2.9%). Before starting immunotherapy, 74% of patients were euthyroid, 18% had clinical or subclinical hypothyroidism, in two cases the previous thyroid status was unknown, and only one patient initiated immunotherapy with subclinical hyperthyroidism. Patients had a mean follow-up of 42.1 ± 36.4 weeks, 61.8% of patients presented asymptomatic transient hyperthyroidism as first alteration 8.7 ± 8.8 weeks after initiating the ICPI, the remaining developed asymptomatic hypothyroidism as first thyroid function alteration, on average 15.7 ± 13.2 weeks after initiating immunotherapy. During follow-up, all patients with hyperthyroidism developed hypothyroidism 6.7 ± 4.2 weeks later. When analyzed separated, those who received ICPI in monotherapy or combination, the combined therapy group presented hyperthyroidism earlier than the monotherapy group (3.4 ± 1.0 weeks vs 12.6 ± 9.1 weeks). No specific treatment was reported for patients with hypertiroidism, however substitutive Levothyroxine was iniciated when hypothyroidism was found. At the end of the follow-up 64.7% continued on Levothyroxine, althought only 48.6% of patients continued on treatment with ICPI. In 31.4% of patients immunotherapy was stopped due to progression of the neoplastic disease and in 5.7% due to immunotherapy related toxicity, but none because of the thyroid function alterations.
Conclusions
In our series, more than half of the patients initially presented with transient hyperthyroidism with subsequent hypothyroidism and the rest with hypothyroidism as first dysfunction, requiring replacement therapy with levothyroxine in most cases. These alterations did not merit the suspension of ICPI. Patients treated with combination of ICPI develop hyperthyroidism earlier compared with patients receiving ICPI as monotherapy.

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GP260

Early low dose rituximab for active thyroid eye disease: an effective and well tolerated treatment

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Background
Thyroid eye disease (TED) is an autoimmune inflammatory disease that can be both disfiguring and potentially sight threatening. Suppression of inflammation in active disease can reduce the risk of visual loss and limit long-term sequelae of the disease. Current disease management involves suppression of inflammation using glucocorticoids. The aim of our study was to evaluate the efficacy of early disease intervention with targeted immunomodulatory therapy to alter the disease course. This paper reports the efficacy of low dose rituximab in reducing clinical activity in TED in a small population.
Methods
A retrospective audit of consecutive patients with active TED at the Oxford Joint Thyroid Clinic (Ox-TED) managed primarily with rituximab. Patients with a VISA clinical activity score of three or more were considered to have active disease and were included in the study. Exclusion criteria included age less than 18 years, pregnancy or breastfeeding, a previous adverse reaction to rituximab, active infection, immunocompromised state or positive HIV or hepatitis serology. All patients were treated with a 100 mg rituximab infusion and 500 mg IV methylprednisolone. Further glucocorticoid or steroid sparing agents were given if clinically indicated. VISA clinical activity score, VISA overall severity score and Oxford Quality of Life score were recorded at baseline and subsequent follow-up visits. TSH receptor antibody (TRAb) levels and B cell subsets were recorded at baseline and following treatment. Any adverse reactions were documented.
Results
Twelve patients were followed up for an average of 6.3 months (1–12 months). VISA clinical activity scores significantly decreased from baseline to most recent

follow up (4.69–1.58, $P<0.001$). VISA overall severity scores significantly reduced by 50% from 12 to 6, $P<0.001$. The average cumulative dose of IV methylprednisolone was 2.25 g, half the cumulative dose recommended by EUGOGO for patients with moderate to severe active TED. Rituximab induced a significant depletion in B-cells ($CD19^+$), $n=11$, $P<0.001$. In those patients with markedly elevated serum TRAb levels >2.5 IU/L ($n=7$) two reduced to moderate levels (0.5–2.5 IU/l) and five remained markedly elevated. A transient infusion related rash was the only adverse effect noted in four patients. QOL scores did not differ markedly before and after treatment.

Conclusion

Low dose rituximab is an efficacious, well-tolerated and safe treatment for active TED; reducing disease activity and allowing reduced administration of systemic steroid.

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GP261

Analysis of serum immunoglobulin G4 (IgG4) levels in euthyroid subjects with autoimmune thyroid disease and goiter in a Single Medical Center in Taiwan

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Immunoglobulin G4-related disease (IgG4-RD) is a newly identified syndrome characterized by high serum IgG4 levels and increased IgG4-positive plasma cells infiltration. IgG4-related thyroiditis (IgG4-RT) was first prescribed based on the immunohistochemistry in 2009. Some of Hashimoto's thyroiditis (HT), Graves' disease (GD) and Riedel thyroiditis were reported to be classified as IgG4-RT based on high serum IgG4 level or histopathological findings. However, the prevalence of IgG4-RT in HT and GD varies in previous reports. There were inconsistent results in the clinical features in IgG4-RT and its relationship to thyroid auto-antibodies. This study is to evaluate serum IgG4 levels in subjects with autoimmune thyroid disease (ATD), and the relationship of serum IgG4 level and thyroid auto-antibodies. A total 185 subjects, including 23 men and 162 women with thyroid diseases were enrolled. 58 subjects had GD in remission, 61 subjects had HT, and 66 subjects had goiter or multinodular as control group. All participants did not receive any anti-thyroid drugs, levothyroxine, or immunosuppressive treatment. The median (interquartile range) serum IgG4 levels were 51.4 (34.4–105.0), 53.4 (32.5–86.8), and 67.5 (38.3–111.0) mg/dl in subjects with GD, HT, and goiter, respectively. There was no significant differences of serum IgG4, IgG levels, and IgG4/IgG ratio between these three groups. There were 9 (15.8%), 5 (8.2%), and 14 (21.2%) subjects had elevated IgG4 levels (>135 mg/dl) defined by serological diagnostic criteria of IgG4-RD in each group, which also showed no statistical differences. Of these 28 subjects with elevated IgG4 levels, 6 (21.4%) were male, which showed a higher male proportion. The mean age was 45.3 ± 12.4 years, which was younger than those with normal IgG4 levels (50.8 ± 11.4 years). However, there were no significant differences in thyroid auto-antibodies, including TSH receptor ($4.3\pm8.7\%$ vs $6.4\pm10.1\%$, $P=0.313$), anti-TPO (122.6 ± 198.7 IU/ml vs 229.6 ± 457.0 IU/ml, $P=0.225$), and anti-thyroglobulin (119.9 ± 264.7 IU/ml vs 217.6 ± 870.5 IU/ml, $P=0.558$) antibodies between subjects with elevated IgG4 and without elevated IgG4. Only one subjects was diagnosed of monoclonal gammopathy of undetermined significance. There was no significant extra-thyroid organ involvement as seen in IgG4-RD in the other 27 subjects. There were no significant differences in serum IgG4 levels, and the prevalence of elevated serum IgG4 level in subjects with GD, HT, and goiter in this study.

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GP262

Thyroid disorders in patients treated with inmune checkpoint inhibition therapy

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Objective

Immune checkpoint inhibitors (ICPI) have become an effective therapeutic option for certain advanced malignant tumours. Immune-related adverse events affecting thyroid function are among the most frequent toxicities. The aim of our study is to determine the prevalence of thyroid disorders in patients undergoing treatment with ICPI.

Methods

Retrospective study including all patients treated with ICPI in our centre, from 07/2015 to 12/2017. Patients were divided into three groups, according to the drug received: Nivolumab, Pembrolizumab or Atezolizumab. Those patients treated with levothyroxine before ICPI therapy were excluded. We used the SPSS program, version 20.

Results

A total of 79 patients were treated with ICPI in our centre; seven of them being treated previously with levothyroxine were excluded. We studied 72 patients, 70.8% men (51/72) with a mean age of 64 ± 8.6 years. 44 patients (61.1%) were treated with nivolumab, 14 patients (19.4%) with atezolizumab and 14 (19.4%) with pembrolizumab. The 54.2% ($n=39$) had lung cancer, followed by melanoma 19.4% ($n=14$), bladder 11.1% ($n=8$), kidney 8.3% ($n=6$), colon 4.2% ($n=3$) and ovarian cancer 2.8% ($n=2$). In 16 patients (22.2%), thyroid side-effects were detected. Two of 16 patients (12.5%) had autoimmune thyroid disease prior to treatment. Mean thyrotropin (TSH) before ICPI therapy was 1.47 (0.39–4.18) mU/l. The most frequent thyroid disorder was subclinical hyperthyroidism in 12/16 patients (75%); the median onset was 5 weeks (range, 1–52). Out of these, 8/12 patients presented transient thyrotoxicosis, 3/12 continued with subclinical hyperthyroidism and 1/12 evolved to hypothyroidism. None of them received antithyroid drugs. 4/16 patients (25%) developed hypothyroidism, without a previous hyperthyroid phase; the median onset was 9 weeks (range, 8-22). 60% hypothyroid patients needed treatment with levothyroxine. No patient needed interruption of ICPI treatment because of thyroid dysfunction. 35.7% of patients treated with atezolizumab developed thyroid disorders, 28.6% of pembrolizumab and 15.9% of nivolumab ($P=0.16$). Indeed, in terms of age, sex and type of tumour, no significant differences were found between those who developed thyroid disorder or not.

Conclusions

In our study, 22.2% of patients with IPCI treatment developed thyroid side-effects. Of these patients, 50% presented transient thyrotoxicosis, 31.3% developed hypothyroidism and 18.7% developed persistent subclinical hyperthyroidism. The median onset was 5 weeks for hyperthyroidism and 9 weeks for hypothyroidism.

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GP263

Thyroid peroxidase antibody-positivity, but not isolated thyroglobulin antibody-positivity, is associated with non-thyroidal autoimmune diseases - a population study of more than 8000 Danes

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Introduction

Autoimmune thyroid disease is associated with other autoimmune diseases. However, most studies are register-based cohort studies or investigate selected patient populations. In a large national cross-sectional population-based study, we investigated positivity of thyroid peroxidase- or thyroglobulin-antibodies (TPOAbs or TgAbs) in association with non-thyroidal autoimmune disease.

Methods

As part of The Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr), two cross-sectional population studies with identical protocol were performed (1997–1998, $n=4649$, and 2004–2005, $n=3570$). Participation involved blood tests and questioning by a medical doctor on history of various diseases. TPOAbs and TgAbs were analysed by radioimmunoassay (DYNOtest, BRAHMS, Germany, cut-off: 60 U/ml). Non-thyroidal autoimmune diseases included rheumatoid arthritis, pernicious anaemia, vitiligo, and diabetes. Logistic regression analyses were adjusted for age, smoking, sex, cohort origin, and familial disposition. Ethical approval and informed consent were obtained.

Results

Of 8105 included participants, 1304 (16.1%) were TPOAb- or TgAb-positive. Hypo- or hyperthyroidism was reported by 2.8 and 2.9%, respectively; 0.6%

reported both. Of the 937 (11.6%) participants reporting non-thyroidal autoimmune disease, 20.3% were thyroid antibody-positive ($P<0.001$ compared to participants without non-thyroidal autoimmune disease), 6.7% reported hypothyroidism, and 4.5% reported hyperthyroidism. In adjusted logistic regression analysis, thyroid antibody-positivity was associated with a significantly higher odds ratio of non-thyroidal autoimmune disease (14.6% vs 11.0%, $P<0.001$, adjusted odds ratio (aOR) 1.3 95%CI:1.1–1.5, $P=0.008$). In participants reporting hypothyroidism, 27.6% reported non-thyroidal autoimmune disease (vs 11.0%, $P<0.001$, aOR 2.5 95%CI:1.8–3.4, $P<0.001$). Hyperthyroidism was associated with nonthyroidal autoimmune disease (17.6% vs 11.3%, $P=0.005$); however, not in adjusted analyses (aOR 1.4 95%CI:0.96–1.9). Excluding participants reporting hypo- or hyperthyroidism, non-thyroidal autoimmune disease was still more prevalent in thyroid autoantibody-positive than -negative participants (13.1% vs 10.6%, $P=0.01$). Among the 190 participants with non-thyroidal autoimmune disease and thyroid autoantibody-positivity, 158 (83.1%) were TPOAb-positive. Participants with TPOAb-positivity combined with TgAb-positivity had similar frequencies of non-thyroidal autoimmune disease as those with isolated TPOAb-positivity (15.3% vs 15.1%). The prevalence among 32 participants with isolated TgAb-positivity was similar to that of thyroid antibody-negative participants (11.9% vs 11.0%, $P=0.62$).

Conclusion

More than 16% of the general population were thyroid autoantibody-positive, which (also without history of thyroid dysfunction) was associated with non-thyroidal autoimmune disease. Especially participants with reported hypothyroidism or TPOAb-positivity, but not those with isolated TgAb-positivity, had increased prevalence of non-thyroidal autoimmune disease. Attention should be paid to polyautoimmunity in patients with hypothyroidism and TPOAbs.

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GP264

Thyroid function in pregnant women; relation to Gestational Diabetes Mellitus (GDM) and Body Mass Index (BMI)

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Objectives

The interplay between thyroid function and metabolic state has been studied in many population subgroups. For pregnant women thyroid and metabolic parameters, including glucose homeostasis, are of great importance for a successful outcome. We examined aspects of thyroid function in relation to GDM and BMI in pregnant women referred to our Department.

Methods

We studied 520 women during 24^{th} – 32^{nd} gestation week. Demographic characteristics were recorded and a 75 gr OGTT was performed. Plasma glucose and insulin levels were measured at time 0'-60'-120'. HbA1c and thyroid parameters (TSH, FT4, FT3, FT3/FT4 ratio) were evaluated at time 0'. Thyroid parameters were subjected to multivariate analysis of variance (MANOVA) with the presence of GDM (GDM vs Normal [N]) and BMI (obese ($BMI \geq 30$ kg/m^2) vs non-obese ($BMI < 30$ kg/m^2)).

Results

Of 520 pregnant women, 226 (43.5%) were diagnosed with GDM according to IADSPG/WHO criteria. GDM women were significantly older (33.6 ± 6.2 vs 29.1 ± 6.8 years) and had greater BMI (30.1 ± 5.4 vs 27.7 ± 5.7 kg/m^2). TSH levels were lower among non-obese women with GDM versus N (1.8 ± 1.0 vs 2.1 ± 1.2 μUI/ml, $P=0.037$). FT4 in obese GDM women was lower than in non-obese GDM and obese Normal (11.7 ± 2.3 vs 12.2 ± 1.8 and 12.4 ± 1.5 pmol/l respectively, $P=0.03$). FT3 levels differed significantly only in the GDM women, between obese and non-obese (4.5 ± 0.6 vs 4.2 ± 0.6 pmol/l, $P \leq 0.001$). In accordance, FT3/FT4 ratio was significantly higher in obese GDM women compared to obese Normal and non-obese GDM (0.39 ± 0.07 vs 0.36 ± 0.08 and 0.35 ± 0.06 respectively, $P=0.03$).

Conclusions

This study shows that (i) GDM is associated with lower TSH levels. (ii) Lower FT4 is associated with both obesity and GDM. (iii) Higher FT3 is associated with obesity in GDM women. (iv) Higher FT3/FT4 ratio is related with the simultaneous presence of GDM and obesity. The pathophysiological mechanisms involved in thyroid hormone metabolism in relation to the presence of GDM and/or obesity need to be further elucidated.

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Thyroid Non Cancer - Benign Thyroid Disease/Treatment

GP265

Nodule size as predictive factor of efficacy of radiofrequency ablation in treating autonomously functioning thyroid nodules

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Background

Radiofrequency ablation(RFA) has been advocated as an alternative to radioiodine and/or surgery for the treatment of autonomously functioning benign thyroid nodule (AFTN). However, only a few studies have investigated the efficacy of RFA on AFTN. Furthermore, these studies are characterized by several biases about patient selection, number of RFA treatments, short clinical and radiographic follow-up. A recent prospective 12-month study has demonstrated that one single RFA treatment was able to withdraw anti-thyroid medication in 50% of the hyperthyroid patients who remained euthyroid afterwards. However, no defined pre-treatment factors able to predict the response to the RFA in Treating AFTN have been clearly identified.

Aim

To evaluate the success rate of RFA to restore euthyroidism in a cohort of adult patients with small solitary AFTN compared to medium-larger ones. Secondary end-points included volume reduction and conversion rate from hot to cold nodules at thyroid scintiscan.

Methods

This was a 24-month prospective monocentric open parallel-group trial. Twenty-nine patients with AFTN were divided into two groups based on thyroid volume: 15 patients with small nodules (<12 ml) in group A and 14 patients with medium nodules (>12 ml) in group B. All patients underwent a single session of RFA and were clinically, biochemically and morphologically evaluated at baseline and at 1, 6, 12 and 24 months after treatment. At the end of the study period, a thyroid scintiscan was performed.

Results

After RFA, there was a larger volume reduction in group A compared to group B ($P<0.001$ for each follow-up point). After RFA, there was greater nodule volume reduction in group A compared with group B ($P<0.001$ for each follow-up point). In group A, there was a greater increase in TSH levels than in group B at 6 ($P=0.01$), 12 ($P=0.005$) and 24 months ($P<0.001$). At 24 months, the rate of responders (subjects with euthyroidsm without metimazole) was greater in group A than in group B (86 vs 45%; $P<0.001$). At 24 months in group A, 86% of nodules converted from hot to cold compared with 18% in group B ($P<0.001$).

Conclusions

This study shows that a single RFA was effective in restoring euthyroidsm in patients with AFTN, mainly in small nodules. Nodule volume seems to be a significant Predictive Factor of Efficacy of RFA in Treating AFTN. Larger prospective studies are needed to confirm our findings.

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GP266

Radiofrequency ablation for benign symptomatic thyroid nodules: evaluation of clinical efficacy

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Purpose

Thyroid nodules are an extremely common occurrence. The aim of the study is to evaluate the results of radiofrequency ablation (RFA) for benign symptomatic thyroid nodules.

Materials and methods

Three hundred and sixty two patients with benign symptomatic thyroid nodules (TIRADS/ Bethesda: TIRADS 2, TIRADS 3/THY 2) were included in this research: 355 women and 7 men. The median age of the group was 48 (24–76). The mean nodule size was 3.5 (1.5–9.5) cm. In 280 cases nodules had solid content, in 82 cases – mixed solid and cystic content. In case of cystic component, aspiration was needed before performing RFA. The mean duration of RFA was 3 (1.5–7) min. All the procedures were performed under local anesthesia with real

time ultrasound control. Technique of dynamic RFA was applied. Internally cooled 1.0–1.2 mm-gauge, 70–100 mm length, 0.5, 0.7, 1.0, 1.5, 2.0 cm active tip electrodes were used. During the procedure permanent control of hoarse voice was carried out to avoid complications. The follow-up period of patients was 1–30 months.

Results

At 1-month follow-up the mean volume reduction was 30 (15–50)%. In further follow-up the reduction of nodule volume was 50% at 6-month follow-up and 75% at 9-month follow-up. RFA was needed to repeat for 19 patients that had an initial nodule size more than 4.5 cm. None of patients experienced any major complications. A surgery was required for four patients whose nodules did not decrease in volume (15%) during the first month follow-up.

Conclusion

RFA is a minimally invasive technique for treatment of benign thyroid nodules with high clinical efficacy.

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GP267

Abstract withdrawn.

GP268

Response to Liothyronine therapy: Efficiacy of therapy and assessment of biochemical and physiological predictors

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Introduction

Levothyroxine is the globally preferred therapeutic compound for primary hypothyroidism. Due to expense and poor efficacy, Liothyronine is not used as first line treatment. This study was formed to answer the ESE's recent call for data on symptomatic response to Liothyronine and predictors of that response.

Method

Patients with failure of symptomatic relief on levothyroxine were invited to try Liothyronine. 23 patients were enrolled. They underwent validated physiological and psychological evaluations which were reviewed at 3, 6 and 12 months for variation and sustainability. Weight, skin quality, mood and fatigue were taken as clinical markers of improvement. Serum thyroid factors were analyzed. Datapoints were then compared with regression analysis to identify any pre-intervention factors that could indicate treatment response.

Results

68% reported an improvement in any clinical factor at month 3 but at month 12, only four patients had sustained improvement from baseline. This was in weight loss >2 kg (2), skin quality (1) and mood (1). Those with weight reduction also improved in at least one other category. No pre-intervention variables examined were linked to therapeutic response, neither age at onset ($r=0.0004$), duration of illness ($r=0.04$), level of Thyroid Perioxidase antibody ($r=0.006$), initial TSH ($r=0.05$), initial t4 ($r=0.14$) or initial t3 level ($r=0.03$). The sustained positive responders showed a tendency to regress towards the mean TSH value, whereas those with transient benefit suppressed.

Discussion

From meta-analyses, we expected a positive response rate varying from 15 to 30% at 1 year. Our data conforms with 17% response across all variables. The most common referral reason for 'therapeutic failure' was low energy and mood, yet only 8% of enrolled patients benefited. Perceived weight has been strongly correlated with symptomology and from our results, a weight loss of >2 kg at 3 months was the only objectively measurable clinical factor to indicate a successful 1 year trial. Supraphysiological dosing with liothyronine is likely the cause of the numerous but transient reported benefits at month 3 given the gradual suppression of TSH in the long term. There remains no pre-intervention indicator identified that would effectively predict response to liothyronine and thus the authors recommend that a decision to offer a therapeutic trial is left to clinician's judgement; that they inform the patient that there is no measurable effect on mood and fatigue; that if there is not >2 kg weight loss at month 3, the medication trial should be withdrawn as there is no evidence to continue.

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GP269

Tailored thyroxine treatment and gastric acid output in humans

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Hypothyroid patients with gastric disorders require a higher dose of oral thyroxine (T4) to reach target serum TSH. *In vitro* evidence supports the notion that the variations of gastric pH may also interfere with T4 dissolution profile. The present study is aimed at confirming in vivo the supposed correlation between the gastric pH, directly measured during endoscopy, and the therapeutic dose of thyroxine using a controlled treatment schedule. A total of 61 tablet T4-treated hypothyroid patients (52 W/9M; median age $=51$ years; BMI $=25.2$) have pledged to take thyroxine in fasting conditions, abstaining from eating or drinking for one hour. Gastric juice for pH evaluation as well as multiple biopsy specimens were collected in all patients during endoscopy. The dose of T4 was calculated in each patient and compared to the one observed in age- and BMI-matched group of patients but positively devoid of gastrointestinal and/or pharmacological interference to measure the excess of T4 required. The results were plotted against the actual pH and the H^+ concentration titrated with $NaOH^-$ in each patient. All patients reached target serum TSH (median $=1.29$ mU/l) but the dose of oral thyroxine required increased along with the rising gastric pH ($r^2=0.1209$; $P<0.0223$) and the diminished H^+ concentration ($r^2=0.1275$; $P<0.0219$). A multivariate analysis revealed that pH act as an independent variable in determining the dose of T4 ($P<0.029$). Noticeably, even the excess of T4 dose (ED) required, plotted against gastric acidity in each patient, was highly correlated with the increased pH ($P<0.001$) and the decreased H^+ concentrations ($P<0.0001$). Patients were then subdivided in two groups, using as cutoff the median value of their pH in the whole sample (2.4; IQ $=1.5$–6.1). Required T4 dose was slightly increased only in eight out of 34 patients (23%) in group A (median pH $=1.52$; median increase $=15\%$). In group B (median pH $=6.36$), on the contrary, 25 patients out of 27 (93%; $P<0.0001$) needed a higher T4 dose and the median increase was huge ($+47\%$). Increased T4 requirement was also unevenly distributed in patients with atrophic gastritis (90%), with pangastritis (73%) and with antritis (40%). The results of this *in vivo* study enlighted a highly significant correlation between gastric pH and the need for thyroxine in humans.

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GP270

Body composition changes during treatment of severe thyroid disorders. Is it always fat?

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Severe thyroid disorder are associated with important metabolic changes. After restoration of euthyroidism, as a result of proper treatment, usually body metabolism also normalizes. Up to date, there are conflicting reports about the changes in body composition of patients during treatment of severe hyperthyroidism and hypothyroidism. The aim of this study was to evaluate the body composition and glucose level changes in subjects affected by Graves disease and autoimmune thyroid disease before the treatment and after achieving

euthyroidism. The study group consisted of 33 patients affected by hyperthyroidism diagnosed with Graves' disease, and 20 patients suffering from hypothyroidism due to autoimmune thyroid disease. In all patients body composition with the use of bioimpendace method, glucose and thyroid-related hormones levels were evaluated at the moment of diagnosis and after restoration of euthyroidism. The mean observation time was 10.5 months for hypothyroid group and 7 months for hyperthyroid group. After restoration of euthyroidism hypothyroid group presented decreased body weight, body mass index, fat-free mass, muscle mass. There was no changes in fat mass and glucose concentration. On the other hand, in the hyperthyroid group achieving euthyroidism was associated with increase in body weight, BMI, fat mass, fat percentage, as well as decrease in glucose concentration. There was no significant difference in muscle mass. The changes in body weight, BMI and fat mass correlated positively with TSH changes and negatively with fT3 and fT4 changes. Muscle mass changes correlated positively with TSH changes and negatively with fT3 changes. To conclude, while increased body mass after the treatment of hyperthyroidism was a result of predominantly fat accumulation, hypothyroid patients lost their body weight mainly due to decreased muscle mass. However, both hyperthyroidism and hypothyroidism causes fat as well as muscle tissue changes.

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GP271

Personalised euthyroid targets based on a deterministic mathematical model

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Research in recent years has shown that biochemically euthyroid levels of thyrotropin (TSH) and serum free thyroxine (FT4) as determined by laboratories may not necessarily equate to clinical well-being of patients. The defined normal range of TSH and FT4 are wide and may differ from patients' optimal range of TSH and FT4. We have previously described a deterministic mathematical model that can predict each patient's unique homeostatic set point, which gives the optimal TSH and FT4 values of each patient. This model is built on a parameterised inverse exponential relationship between TSH and FT4. In this retrospective study of 142 patients who had undergone thyroidectomy, we used the model to compute the predicted TSH and FT4 values based on thyroid function tests obtained post-thyroidectomy. The predicted values were then compared with the average TSH and FT4 obtained pre-thyroidectomy, when the patients were clinically euthyroid. Bland-Altman analysis of the differences between the predicted values and the average pre-thyroidectomy values shows that there is a mean difference of 0.15 mU/l, 95% CI (−0.03, 0.34), between the predicted TSH and average pre-thyroidectomy TSH and a mean difference of 2.87 pmol/l, 95% CI (2.55, 3.24), between the predicted FT4 and average pre-thyroidectomy FT4. Despite minor differences between the predicted values by the model and the average pre-thyroidectomy values of the patients, our mathematical model is able to narrow the range at which a patient can be considered as being euthyroid. Therefore, the personalised euthyroid targets derived from the model is able to provide clinicians with more guidance in managing patients who remain symptomatic despite having normal TSH or FT4 values.

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GP272

US-guided percutaneous microwave ablation for benign thyroid nodules: a prospective multicenter study

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Purpose
To evaluate the clinical outcomes of percutaneous MWA in treating BTNs under US guidance with a prospective multicenter study.

Materials and methods
From January of 2013 to December of 2015, the total number of 603 patients with 664 benign thyroid nodules (BTNs) at four participating institutions in China was enrolled in the multicenter study. Before ablation, the mean maximal diameter and the mean volume of the target nodules were 2.92±0.93 cm (ranged from 2.0 to 6.3 cm) and 7.72±9.16 ml (ranged from 0.38 to 70.16 ml), respectively. The clinical outcomes of safety and efficacy were evaluated and analyzed by SPSS 22.0 during follow-up period.
Results
For evaluation of efficacy, compared to those in baseline, the mean maximal diameter and the mean volume of the ablated BTNs significantly decreased with the volume reduction ratio (VRR) of 64.4±43.5%, 78.4±48.2%, 82.5±49.7%, and 81.1±70.4% at 3, 6, 12 months and last follow-up, respectively. The vascular, symptomatic and cosmetic scores related the target nodules statistically improved after ablation. For evaluation of safety, the major complications included cervical nerve injuries in 16 patients (injuries of recurrent laryngeal nerve in 15 and sympathetic nerve in one) and nodular ruptures in four patients. The incidences of minor complications and side effects were 5.8% (35/603) and 4.6% (28/603), respectively.
Conclusion
To draw the conclusion of the prospective multicenter study, US-guided percutaneous MWA is a safe and effective method for the treatment of BTNs in selected patients.

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GP273

Abstract withdrawn.

GP274

Reduced quality of life and persistent complaints in treated hypothyroid patients

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Background
Hypothyroidism is a common endocrine disorder and the standard treatment is replacement therapy with levothyroxine (LT4). Although many hypothyroid patients improve upon treatment with LT4, a proportion seems to experience residual hypothyroid complaints despite treatment, even when plasma TSH and FT4 are within reference ranges.
Methods
Using an on-line survey we investigated i) the health-related quality of life (QoL) (ThyPRO), ii) the activities of daily living (SF-36), iii) hypothyroid-related symptoms (ThySHI) in diagnosed, treated hypothyroid patients (>18 years, treated >6 months) and control persons (without thyroid disease, >18 years). In patients, the time course of symptoms from diagnosis until 3 years was asked (retrospectively, ThySHI). Patients and control persons were recruited by e-mails from patient organizations, posters in pharmacies and health centers and Twitter/Facebook. For data analysis (ThyPRO, 0–100 scale, *t*-test; daily functioning, 1–5 scale and ThySHI 0–3 scale, Mann-Whitney; time course symptoms, Friedmann-Dunnett; confounding factors, ANCOVA) IBM SPSS 24 was used.
Results
In this cohort consisted of 1667 patients (mean duration of illness 12.2± s.d. 9.9 years) and 275 controls. Treated hypothyroid patients had i). a significant decrease in health-related QoL and all domains (fatigue, vitality, cognition,

anxiety, depressivity, emotional susceptibility, social life, daily life), as compared to controls (mean total QoL 39.9 vs 19.1 resp. and all domains $P<0.001$), ii). Significantly more impairment with activities of daily living ($P<0.001$), and iii). significantly higher scores for symptoms related to hypothyroidism, as compared to control persons (all $P<0.01$). Symptoms generally decreased after 3 years of treatment, with fatigue, reduce daily functioning, coldness, muscle pain/cramps and being overweight as the most intense residual complaints. Many patients (78.5%) reported having complaints despite taking thyroid medication and reported not feeling well (77.8%) while their blood values were within range. TSH level, age, gender and duration of illness did not significantly affect total QoL, whereas the M3 comorbidity index did. Desiccated thyroid hormone users (9.4%) had a significantly better mean total QoL than LT4 users (90.5%) (36.0 vs 40.6, $P=0.003$).

Conclusions

Persistent complaints, such as reduced health-related quality of life, reduced daily functioning, and residual hypothyroid related symptoms, are common in this group of hypothyroid patients despite replacement therapy. Caregivers should be aware that persistent complaints can be present in treated hypothyroid patients, despite following current guidelines, and that these remaining symptoms may affect their quality of life and daily functioning.

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Poster Presentations: Adrenal and Neuroendocrine Tumours

Adrenal cortex (to include Cushing's)

P1

Congenital adrenal hyperplasia in lady with severhirsutism and virilization due to 3B-hydroxysteroid dehydrogenase deficiency

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A 30-year-old woman pakistani patient was admitted to king Abdulaziz University hospital in Jeddah, Saudi Arabia with history of severe abdominal pain, vomiting and hypotension. She was born with Ambiguous genitalia and operated at age 8 years. She has severe hirsutism, with score of 18 and virilization. There are no family history of congenital adrenal hyperplasia. Physical examination showed her height was 151 cm and weight 42 kg. For evolution of hirsutism and virilization. Endocrinological data showed heigh DHEA-S and urinary 17 KS levels were moderately increased, while plasma testosterone, androstenedione and urinary 17 OHCS levels were normal. CT the abdomen and pelvis were normal. The patient had increased plasma 17-hydroxypregnenolone and DHEA concentrations in response to ACTH. 17-hydroxypregnenolone is 6.2 ng/ml and increase up to 10.5 30 minute after ACTH stimulation. DHEA-S is 5.3 ng/ml and increase to 13.8 nm/ml after ACTH stimulation. She had increased ratios of 17-hydroxypregnenolone of DHEA to androstenedione. After administration of 2 mg dexamethasone twice daily, all glucocorticoid and androgen levels including their metabolites decreased, indicating that the excessive androgen was derived from the adrenal glands. BMD showed severe osteoporosis with T score – 3.5. Patient was treated with dexamethasone,1 mg twice daily, Densoumb 60 mg Im once every 6 month as well social and psychological support. The patient felt that hirsutism was improved; the shaving frequency decreased from twice a day to once a day and the texture of the hair became softer and less coarse.

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P2

Endogenous stimulation in adrenal venous sampling (AVS) in differential diagnosis of primary hyperaldosteronism (PA)

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Relevance
Due to numerous causes of PA, AVS allows differentiating variant nosological forms of PA. The importance of differential diagnosis is due to the fact that surgery is reasonable only with unilateral variant of PA, while in idiopathic hyperaldosteronism surgery isn't a method of choice.
Purpose
To assess the diagnostic possibilities of using AVS against the background of endogenous stimulation of adrenocorticotropic hormone (ACTH) in the early morning hours for choosing the method of treatment of PA.
Materials and methods
Fourty-eight patients were prospectively enrolled for AVS, average age 40y.o. (2011–2017), with arterial hypertension, adrenal glands lesion according to CT and laboratory confirmed PA (elevated aldosterone-renin ratio and postinfusion level of aldosterone). Average size of lesion was 2 cm (1.5–3), density from −1 to +10HU, and with bilateral damage, the second gland was hyperplastic (about 10mm). We measured reliable level of selectivity gradient as 3:1, then we calculated the result of lateralization gradient, and more than 2 shows unilateral aldosterone production, less than 2 shows bilateral aldosterone production.
Results
According to CT, unilateral macrogyperplasia was detected in 13 patients (27% of total), all of them were confirmed to have unilateral hyperproduction of aldosterone according to AVS. Unilateral microhyperplasia was detected in 12 patients (25%); among them 4 (8.3% of total) was confirmed unilateral hyperproduction according to AVS. It was detected that bilateral macrogyperplasia was in 23 patients (48%), of which 6 patients (12.5% of total) showed bilateral hypersecretion of aldosterone.
Conclusion
CT didn't correspond with the results of AVS in 4.1% cases. In absence of AVS, surgery in these patients wouldn't have been implemented. In 20% cases was identify bilateral hyperproduction and relying only on CT, adrenalectomy could be done unreasonable. Given our data, it can be concluded that AVS is an important step in the differential diagnosis of PA.

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P3

Congenital adrenal hyperplasia in 46xx male

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Disorders of sex development create medical and social dilemma. Maleness with XX genotype is a rare genetic condition affecting one in 24,000 new-born males. Characterized by a spectrum of clinical presentation, ranging from normal male genitalia to ambiguous sex.
Case report
A 31 years old patient with ambiguous genitalia raised as a male. He came to our endocrinology clinic to stabilize his male identity by surgical correction, no parental consanguinity. The patient has five brothers. Two of them were born with sexual ambiguity and both died at the age of 6 months due to asthenia, weakness and, failure to thrive. His medical suffering started since birth when his mother discovered that he was born with an empty scrotum. He underwent a surgery for undescended testes at the age of 2. The surgeon didn't find the testes, but when the ultrasonography was done, it revealed the presence of a uterus. He had his adrenarche at the age of 12 (well developed axillary, pubic and chest hair). His male type of boldness at the age of 17. Physical examination showed Height: 162 cm, Weight: 63 kg, BMI: 24.0 kg/m^2. He possessed coarse hair all over his body including auxiliary, pubic and chest area. Genital examination revealed Microphalus (enlarged clitoris: size is 7 cm) with penoscrotal hypospadias empty Scrotum. The results of laboratory analyses were as follows: follicle-stimulating hormone: 4.6 mIU/ml (N:0.7–11.1), luteinizing hormone: 3 mIU/mL (N: 0.8–7.6), and testosterone: 2.2 ng/mL (N: 2.5–8.4 mg/mL). Estradiol (E2): 24.2 pg/ml (N:15–56), Serum DHEA: 7.1 ng/ml (M&F 0.2–9.8). Androstenedione: >10 ng/ml (N:0.75–2.05), 17 hydroxyprogesterone: >4000 ng/dl (N: <77 ng/dl) Serum sodium: 144.0 mmol/L (N:132.0–145.0),Serum potassium: 3.6 mmo/L (N:3.5–5.1). karyotype analysis showed 46,XX. Abdominal pelvic U/S non visualized testis, Both ovaries are seen functioning with follicles noted, The uterus seen with endometrial line. Bulky right supra renal gland, MRI abdomen revealed Both suprarenal glands are diffusely enlarged: eliciting intermediate T1 and T2 signal intensity with no focal lesions. Classic congenital adrenal hyperplasia (21-hydroxylase deficiency) was diagnosed, the patient received a one month course of 15 mg hostacortin however he refused to continue treatment.
Conclusion
21-hydroxylase deficiency should be considered in the differential diagnosis of cases presented with ambiguous genitalia in early childhood, treatment decision must be made for each individual. Considering social, psychosexual development, psychological and cultural factors.

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P4

Diagnostic difficulties of Pseudo-Cushing states in women: about 24 cases

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Introduction
Differentiation between mild Cushing's syndrome (CS) and Pseudo-Cushing syndrome (PCS) can be extremely difficult. A Pseudo-Cushing state can be defined as a part or all of the clinical features that resemble a true CS with some evidence of hypercotisolism but the resolution of the underlying primitive state results in the disappearance of this Cushing state-like. The aim of this work was to describe the diagnostic difficulties of 24 cases of PCS.
Patients and methods
A descriptive study of 24 women referred to the endocrinology department for suspicion of CS.
Results
The mean age of the patients was 33.3 years old. Nine patients were followed for hypertension, 7 for type 2 diabetes and 2 for depression. On examination, the average body mass index was 41.43 kg/m^2. The average waist circumference was 118.5 cm. With respect to CS elements, 83.33% of patients had truncal obesity, 29.16% had facial erythrosis, 16.66% had buffalo hump, 16.66% had hirsutism, 8.33% had acne, 16.66% had purple stretch marks and 16.66% has intertrigo. No patient had muscular atrophy or bruising. In the biology, the fasting glucose level was 1.41 g/L on average, the mean triglyceride level was 1.25 g/L and the mean HDL-cholesterol level was 0.44 g/L. About one third of these patients had a metabolic syndrome. The overnight dexamethasone suppression test was negative in 50% of our patients whereas the standard 2-day dexamethasone suppression

test was positive in all our patients which allowed us to retain rather the diagnosis of a PCS. Abdominopelvic ultrasound showed hepatic steatosis in seven patients and ovarian dystrophy in one patient. Bone densitometry was requested in two patients with a normal bone profile for age.
Discussion and conclusion
Pseudo-Cushing states share many of the characteristics of CS, including overproduction of cortisol. The hypercotisolism of PCS is caused by the increased activity of the CRH neuron which stimulates the production and release of ACTH. Despite the fact that some symptoms are more specific to CS than PCS, the diagnosis depends always on laboratory results.

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P5

Abstract withdrawn.

P6

Is adrenocortical carcinoma in children a different spectrum?

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Background
Adreno cortical carcinoma (ACC) is a rare malignancy associated with aggressive biological behavior and poor outcome. The reported incidence in literature is about approximately two cases per million population's.These tumors might be functional or non-functional depending on their ability to secrete various adrenocortical hormones. ACC occurring in children and adults show distinct characteristics and there is not much literature regarding the differences. Since it is a rare disease large sample size is a difficulty.
Aim
The aim of this study was to study Clinico-pathologic profile and outcome of ACC occurring in children and adults.
Methods
This study (January 1990–June 2017) was carried out in a tertiary referral centre, included 60 patients with Adreno cortical carcinoma. Patients aged 18 years or more were classified as adults and rest as children. Demographics, clinical profile, hormonal profile, details of surgical procedures, histology and/ or cytology reports and follow up findings were noted. Survival analysis was performed using Kaplan Meir method and significance of various factors was calculated by Cox regression analysis. Various factors and outcome were compared. A P value of less than 0.05 was considered significant.
Results
There were 20 children and 40 adults. Mean Age was 8 ± 5.7 (M: F = 1: 2.1) and 44.4 ± 15 years (M: F = 1:1.1). Prevalence of functioning tumors was significantly high in children (85 vs 40% $P = 0.001$), and Incidentaloma in adults (6.3 vs 51.7% $P = 0.05$). Tumor stage distribution at presentation was comparable in both groups. 85% children and 62.5% of adults were operated. The mean tumor size and weight were 10.9 vs 13.7 cm ($P = 0.08$), and 392.9 vs 892.9 gm ($P = 0.24$) respectively. Adults had better five year overall survival (OS) than children. On univariate analysis stage of disease ($P = 0.008$), surgical intervention ($P = 0.004$), Weiss score ($P = 0.006$) and hormonal secretion ($P = 0.04$) were significantly associated with OS in adults but not in children. No factor was found significant on multivariate analysis.
Conclusions
Except for high prevalence of functioning tumors in children, there was not much difference in clinicpathologic attributes. Larger studies and multicentre studies are needed so that guidelines can be framed and diverse management can be avoided.

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P7

Travelling distance and support group participation in patients with chronic adrenal insufficiency

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Adrenal crisis is a life-threatening complication in patients with adrenal insufficiency. In order to prevent critical situations, patients have to increase their glucocorticoid dose in distressing situations. Continuous education of patients concerning dosage adaption in challenging situations seems to be important for long term management. As previously shown, both acute illness and emotional stress may lead to critical situations. In every outpatient visit patients should be able to address dosage problems concerning their daily living. In addition to that support group meetings and educational courses for emergency management for patients with chronic adrenal insufficiency seem to be a good possibility for discussing challenging situations. We wanted to know whether patients are interested in support group meetings and whether they already attended. Additionally, we wanted to know what distances patients are willing to travel to attend educational meetings. We decided to ask patients before attending our educational program teaching management of critical situations for patients with any kind of chronic adrenal insufficiency including self-application of parenteral hydrocortisone. We included 43 patients attending our educational program in 2017. Most of the patients (88%) had never attended a support group meeting. Many of those stated that they did not know about any known offer of a support group meeting (74%), while 8% mentioned long travelling distances. Only two patients were not interested in support group meetings. Two more were recently diagnosed and were not yet able to attend any meeting. Nearly all patients (95%) had never attended a special education program teaching emergency situation management before, although 45% had suffered from an adrenal crisis before. For attending our education program mean travel distance was 40 km, while maximum travel distance was 155 km. In summary, only a few patients are not interested in attending support group meetings. Most of them are willing to participate but lack information about any offers. For attendance patients tolerate longer travelling distances (mean travel distance 40 km). We recommend informing all patients about self-support groups and educational meetings on a regular basis.

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P8

Abstract withdrawn.

P9

Evaluation of tumor size and hormonal status of elderly with adrenal incidentaloma

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Incidentalomas (AI) are clinically inapparent adrenal masses. Patients present hormone excess or mass effect, but part of them is clinically silent. They are discovered inadvertently in the course of diagnostic testing or treatment for other clinical conditions. The aim of the study was to investigate the clinical value of tumor size and hormonal status of elderly patients with adrenal incidentaloma (AI).
Subjects and Methods
Forty-four elderly with AI was diagnosed AI discovered by magnetic resonance (MR). The demographics of patients, imaging features, functional status and histological results were evaluated, retrospectively.

Results
Thirty-two (72.7%) of the patients were females and 12 (27.7%) of them were males. Mean age of the patients was 69.1 ± 13.0 years. 5 (11.3%) of the patients' age were ≥ 75 years. Mean volumes of AI found to be 3.12 ± 0.7 cm. In 6 (50.0%) of the elderly male with AI, sizes of tumor found to be ≥ 3.5 cm and were operated. Histological findings in operated male were myelolipoma (two male patients) and metastatic epidermoid cancer originating from lung (two male patients). Mean levels of Dehydroepiandrosterone (DHEAS), cortisol, vanil mandelic acid (VMA), aldosteron, 17-hydroxyprogesterone (17-OHP) were found to be 289.3 ± 89.2 (ng/ml); 15.3 ± 3.56 (μg/dl); 4.0 ± 1.1 (mg/24 h); 121.1 ± 21.3 (pg/mL); 1.0 ± 0.3 (ng/ml) respectively.
Conclusion
The frequency of AI in the female elderly was higher than thats of male elderly. However, mean levels of tumor size in male elderly than thats of female elderly. This is a preliminary report, future studies are needed.

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P10

Evaluation of adrenal function in Cushing's syndrome model rats

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Cushing's syndrome is caused by cortisol-secreting adrenocortical adenoma. Surgical resection of cortisol-secreting adenoma results in secondary adrenal insufficiency in most cases. The main mechanism of adrenal insufficiency is that the residual adrenocortical tissue becomes atrophied as a result of chronic suppression of the hypothalamic-pituitary-adrenal (HPA) axis by excessive cortisol levels. Therefore, we have analyzed Cushing syndrome model rats following the previous year's report in order to develop a new treatment that promotes early functional improvement in postoperative remaining adrenal glands. Increase in blood pressure (117 ± 16 mmHg), decrease in body weight (380 ± 25 g), suppression of ACTH (43 ± 18 pg/ml) and reduction of adrenal weight (14.4 ± 1.7 mg) were significantly confirmed in dexamethasone-treated rats ($n = 8$) compared to the control group ($n = 8$), and a decrease in ratio of adrenal cortex to medulla was also confirmed. These results were similar findings in the previous year. In this experiment, adrenal function was evaluated by reverse transcription PCR (RT-PCR) of adrenal gland tissue and measurement of mRNA. The expression level of *CYP11B1* mRNA was calculated as cortisol productivity, and the expression level was significantly decreased in the dexamethasone administration group (0.09) compared to the control (1.00). It was confirmed that the hormone secretion ability of the adrenal cortex was significantly decreased endocrinologically in the model rat as compared with control rats. Our group is now conducting experiments to evaluate the improvement of remaining adrenal function by administering synthetic ACTH formulation.

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P11

Does Hemodialysis (HD) affect the overall testosterone (T) and luteinizing hormone (LH) levels in T-treated hypogonadal Congenital Adrenal Hyperplasia (CAH) male with associated chronic kidney disease (CKD)? A pilot single center matched case report

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Introduction
CAH is among the most common inherited metabolic disturbances, caused by Ar mutations of genes that encode enzymes involved in the adrenal steroids synthesis. Male hypogonadism and CKD can complicate the course of CAH. Additionally, HD can influence the CAH management by unpredictable effects of ultrafiltration on the levels of administered drugs. The aim of our study is to demonstrate the influence of HD on LH/T levels of eugonadal male as well hypogonadal male with CAH under T-substitution, both with CKD.
Material and Methods
CAH 38-years-old male and age/gender-matched control has had a regular thrice-weekly maintenance HD on the same device (*Gambro AK200 Ultra S*) in Zemun Clinical Hospital. CAH hypogonadal male is under parenteral T 250 mg (D1) on regular 3-weeks intervals. According to approved study protocol, blood samples were collected in determined points (D0, 1, 7, 14, 21 for T-treated and D0 and 21 for control patient) for the purpose of T and LH measurements before and after HD session. Analyses were performed by *DXI-600 Beckman Coulter* device.
Results
Obtained data are showed in Table.

Hormones	Before T (D_0)		D_1		D_7		D_{14}		D_{21}	
	<HD	>HD	<HD	>HD	<HD	>HD	<HD	>HD	<HD	>HD
LH_C (1.2–8.6) [U/l]	6.52	6.90							6.20	5.66
T_C (6.07–27.1) [nmol/l]	7.66	7.44							8.63	7.59
LH_{T_t}	18.61		22.74	26.51	1.72	2.17	0.86	0.41	2.91	2.79
T_{T_t}	5.85		15.97	12.66	12.04	17.33	11.11	11.11	7.89	9.23

HD = Hemodialysis; < - before HD; > - after HD; D = day; C = control patient; T_t = testosterone-treated patient.

Discussion
Our results demonstrated the regular male age-related LH/T levels in control examinee, with no significant change after HD sessions. T level at D0 lower than normal revealed that patient was not T-overdosed (i.e. regarding previous T-dose and interval of administration). The expected trends of T-levels increase and LH-levels decrease were registered in initial control points of T-treated patient. However, the other way round trend of the observed hormone levels were registered in later control points in the same patient. Additionally, there were no extreme changes in the LH/T levels before and after HD sessions at control points in both examinees. The ultimate control point hormone levels of both examinees were in the reference range.
Conclusion
HD does not significantly influence LH/T levels in eugonadal and T-treated hypogonadal CAH patient, both associated with CKD. The LH/T levels are reliable markers of the quality of T-substitution in HD-treated patients.

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P12

A rare case of Cushing's syndrome due to adrenal adenoma complicated by familial adenomatous polyposis

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Introduction
Adrenal adenoma is one of the extraintestinal lesions associated with familial adenomatous polyposis (FAP). Only four cases of Cushing's syndrome due to adrenal adenoma complicated by FAP, including ours, have been reported to date.
Case report
A 37-year-old woman presented with pretibial edema and hirsutism. She was diagnosed with FAP at 8 years old. She had undergone resection of craniopharyngioma at 10 years old and repeated removal of desmoid tumors. Polyposis was observed in the stomach, duodenum, upper jejunum, and large intestine. Polypectomy was performed for a large intestine lesion. Her mother and younger sister also had FAP, but her mother had died of colorectal cancer. The patient had developed hypertension and menstrual abnormalities at the age of 35 years. She also had diabetes (HbA1c 7.7%) and was obese (BMI 31.1 kg/m^2). Upon physical examination at our hospital, facial fullness, morbid obesity, a buffalo hump, striae, pretibial edema, subcutaneous bleeding spots, and hypertrichosis were detected. Laboratory assays revealed hypercortisolism (17.2 μg/dl), indicating the circadian rhythm loss of cortisol secretion, no suppression in the low- and high-dose dexamethasone suppression tests, and high levels of urine free cortisol (240 μg/day). ACTH levels were always

suppressed (< 2 pg/ml). There was no excess catecholamine, and the renin-angiotensin system was normal. CT revealed a left adrenal mass measuring 5.3× 5.2×4.7 cm. She underwent left laparoscopic adrenalectomy. She was diagnosed with Cushing's syndrome owing to the left adrenal gland tumor, which was pathologically diagnosed as adenoma. Genetic analysis of APC via the direct sequence method showed a mutation in codon 1517 (CAG (Gln) → TAG (STOP)), which has been reported in patients with an extraintestinal manifestation of FAP.
Discussion
Brain tumors, papillary adenocarcinoma of the thyroid, hepatoblastoma, retinal pigment epithelium hyperplasia (CHRPE), osteoma, desmoid tumors, and adrenal adenomas are known extraintestinal manifestations of FAP. FAP is an autosomal dominant hereditary disease that occurs due to an *APC* mutation on the chromosome locus 5q21-22. *APC* consists of 15 exons and 2844 codons. The highest cumulative mutation frequencies in extra-colonic manifestations are found between codons 976–1067 and 1310–2011, for example, desmoid tumors, which frequently show mutations in codons 1309–1580. However, no genotype-phenotype correlations have been established for adrenal adenoma or functional adrenal adenoma. This association will likely be elucidated with more reports like this case study.

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P13

Hypoglycemic coma as first manifestation of primary adrenal insufficiency in a septic patient with severe hypokalemia and hypomagnesemia

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Introduction
Adrenal crisis due to primary adrenal insufficiency may result in severe morbidity and mortality if undiagnosed or ineffectively treated. Main manifestations are hypotension (>90%), hyponatremia (70–80%), and hyperkalemia (30–40%), while hypoglycemia is rare. An unusual case of a septic patient with hypokalemia and hypomagnesemia with hypoglycemic coma as first manifestation of acute adrenal insufficiency is presented.
Case presentation
A 51-yr-old woman, with tetraparesis after a cervical spine fracture 20 years ago, was admitted to Intensive Care Unit for septic shock due to osteomyelitis of the right hip. She received empirically several antimicrobials such as vancomycin, amikacin, daptomycin, tigecyclin and high doses of fluconazole. After clinical improvement, she was transferred to the *Department of Orthopedics,* where she started to complain of anorexia, fatigue, nausea and polyuria. Laboratory tests revealed normal serum sodium, hypokalemia and hypomagnesemia due to increased urine losses of respective cations, nephrogenic diabetes insipidus and renal tubular acidosis. A month later, she had two episodes of seizures with subsequent loss of consciousness. Her blood pressure was low (85/56 mmHg). Laboratory evaluation showed very low blood glucose levels, confirming the diagnosis of hypoglycemic coma. Hormonal evaluation revealed low levels of cortisol and aldosterone with high levels of ACTH and renin, indicating acute adrenal failure. Abdominal CT scan showed normal size adrenal glands, with no sign of adrenal hemorrhage. Investigation for infections such as tuberculosis, fungi, CMV and HIV, commonly associated with primary adrenal insufficiency, was negative. Previous fluconazole therapy was considered as the most possible etiology of adrenal dysfunction. Hydrocortisone replacement treatment led to restoration of blood glucose and blood pressure levels. It is remarkable that, despite adrenal insufficiency, severe hypokalemia and the associated nephrogenic diabetes insipidus, resisted and were both restored only after correction of serum magnesium.
Conclusion
Fluconazole in high doses may inhibit adrenal steroidogenesis and may cause adrenal failure. In addition, antibiotics commonly used in acutely ill patients, such as amikacin, may cause renal damage, with electrolyte disturbances, such as hypomagnesemia and hypokalemia. The diagnosis of acute adrenal failure caused by fluconazole may be obscured in septic patients with antibacterial-induced renal damage. Sudden appearance of severe hypoglycemia in such patients must be taken into account as a sign of adrenal insufficiency and must be investigated and treated appropriately.

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P14

Preoperative treatment with metyrapone in patient with Cushing's syndrome due to adrenal adenoma: a pilot prospective study

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Background and objectives
Metyrapone has been approved for the treatment of patients with Cushing's syndrome from all causes, but only few retrospective clinical studies are available. The aim of our study was the prospective assessment of metyrapone as pre-operative treatment.
Methods
Before adrenalectomy, 7 patients with ACTH-independent Cushing's syndrome due to adrenal adenoma were prospectively treated with metyrapone for 3 months, with endocrine work-up and clinical evaluation at screening and at predefined evaluation time points (Day 14, 31, 48, 65, 82).
Results
In all patients, UFC levels decreased up to normal range from baseline to Day 82 [609 (188–1476) vs. 69 (28–152) nmol/24 h, $P<0.02$], with a reduction of serum and salivary cortisol levels, and no significant increase of plasma ACTH and serum DHEAS levels. Clinical improvement was reported on quality of life [+16.7 (+4.2;+52.00) points, $P<0.04$) and pressure control [systolic pressure, −25 (−52;−10) mmHg, $P<0.01$; diastolic pressure, −16 (−50;+2 mmHg), $P<0.03$)]. No significant change in weight, electrolytes, glycemic and lipid profile was reported. Although in women a significant increase of testosterone and androstenedione was reported, no worsening of clinical hyperandrogenism was observed. All drug-related adverse events (nausea, fatigue, low grade fever, edema of lower limbs and facial rash) were grade 1 or 2 and generally transient.
Conclusions
This prospective pilot study demonstrated that metyrapone is effective in normalizing biochemical and clinical parameters in patients with Cushing's syndrome due to adrenal adenoma before surgical intervention, with minimal side effects.

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P15

Clinical features of adrenal incidentalomas

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Introduction
Adrenal incidentalomas (AI) are tumours revealed during radiological procedures in patients without previous suspicion for adrenal disease. This study was conducted to determine the frequency of functional AI.
Patients and methods
Thirty-eight patients with AI were included in the study. The following parameters were considered: patient age, gender, size and location of the tumour, and radiological characteristics of adrenal masses. In order to determine hormonal activity of incidentalomas the following tests were done: basal cortisol values and day-night rhythm, adrenocorticotropic hormone (ACTH) overnight dexamethasone suppression test, vanillymandelic acid (VMA) in 24 h urine, electrolytes, haematocrit (HCT), acid-base status, oral glucose tolerance test (OGTT) and chromogranin A (CgA).
Results
Patients consisted of 22 females (57.89%) and 16 males (42.1%) aged between 23 and 78. The highest incidence was in sixth decade (34.21%). Regarding the tumour localisation, 60.53% were found in the left ad-renal gland, 34.21% were visualised in the right, and 5.26% of the patients had bilaterally AI. The majority of analysed lesions were 1–4 cm in size (86.84%). Based on CT scans features, only two patients were highly suspicious of malignant AI. Hormonal evaluation showed that 32 patients (84.21%) had non-functional adrenal lesions. Among 6 patients with verified AI functional activity, 3 had pheochromocytomas, 2 were

diagnosed as Cushing's syndrome and one patient had aldosterone-producing adenoma. Adrenalectomy was performed in 9 patients. Histopathological examination confirmed suspected hormonal activity in 6 patients, adrenocortical carcinoma in one patient and secondary deposits due to bronchial carcinoma in one patient.

Conclusion

Along with technology advances detection of AI is significantly increased. Two crucial tasks for physician are: 1. to distinguish functional from nonfunctional adrenal tumour and 2. to conclude whether it is benign or malignant one. Even though the frequency of functional AI is low and malignant AI even lower, thorough diagnostic procedures should be conducted in order to triage patients for surgical treatment.

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P16

Rare incidence of primary adrenocortical carcinosarcoma: a case report

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Introduction

Adrenal tumors are common tumors with a prevalence of around 3% in a population over the age of 50 years. In contrast, adrenocortical carcinoma (ACC) is a rare malignancy (incidence 1–2 per 1 million population) with a heterogeneous presentation and a variable but generally bad prognosis. Patients present with evidence of adrenal steroid hormone excess in approximately 60% of cases.

Case report

A 49-year-old woman with symptoms of facial swelling, weight gain; predominantly abdominal, appearance of hair on face and neck, high blood pressure, bruising and insomnia during the last four months. In addition, polymenorrhoea in the last two menstrual cycles. No medical history of interest except the start of antihypertensive treatment in the last year. The patient exhibited clinical features associated with excessive steroid hormone or catecholamine levels. Thus, blood tests with an adrenal hormone profile were requested:

low dose dexamethasone suppression	26 μg/dl
24-hour urinary cortisol	686 μg/24 h
ACTH	<5 pg/ml
Metanephrines	93μg/24 h
Normetanephrines	24 μg/24 h
Adrenalin	not detectable
Dopamine	109 μg/ 24 h
Aldosterone/ plasma renin activity	<30

These clinical symptoms and analytical alterations led to the discovery of a 8x8x11 cm heterogeneous hypoechoic left adrenal mass on an abdominal magnetic resonance. After surgery adrenal cortical carcinoma with areas of necorsis and hemorrhage is confirmed. It exceeded adrenal gland and reached peripancreatic tissues. It presented perineural invasion but no vascular invasion. Negative immunostaining for steroidogenic factor 1, melanA markers and chromogranin A was confirmed. The surgery was completed with right suprarenalectomy, tail and body pancreatic resection and nodulectomy of segment three of the liver (it confirmed intraoperative metastasis). The treatment regime usually depends on cancer stage. Two major staging systems are used: the American Joint Committee on Cancer (AJCC) TNM staging system and the ENSAT staging system(European Network for the Study of Adrenal Tumors). The ENSAT staging system is essentially the same as the AJCC system, but reserves stage IV only for tumors with distant metastasis. In our patient, we are in stage IV, pTN3NxM1 and following the criteria of ENSAT he had started mitotane-EDP (doxirubicin-cisplatin-etoposide). Moreover, she is taking hidroaltesona 20-10-10 mg daily because there is an increase in cortisol metabolism secondary to mitotane.

Conclusion

In advanced ACC, mitotane is still the standard of care. However, most patients will experience progress and will require rescue therapies due to the delayed diagnosis and aggressiveness of the ACC. Thus, new treatment concepts are urgently needed.

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P17

Clinical and biochemical outcomes in surgically treated patients with primary aldosteronism. A multicentric retrospective study

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Background

Although unilateral primary aldosteronism (PA) is the most common surgically correctable cause of hypertension, no standard criteria exist to classify surgical outcomes. The Primary Aldosteronism Surgical Outcome (PASO) study was an international project to develop consensus criteria for outcomes and follow-up of adrenalectomy for unilateral PA.

Objetives

To determine the proportions of patients achieving complete, partial, or absent clinical and biochemical success in accordance with the consensus criteria and to identify preoperative factors associated with outcomes in surgically treated patients with PA in three centers from Castilla La Mancha (Spain).

Design

Multicentric retrospective observational study.

Methods

We analysed clinical data from 53 patients with a diagnosis of unilateral PA who underwent surgery between 1999 and 2016, of whom 41 had postsurgical biochemical data. Treatment was guided by computed tomography (CT) scans**.** Preoperative adrenal vein sampling (AVS) was performed in 15 patients. We used the PASO standardised outcomes criteria (complete, partial, and absent success of clinical and biochemical outcomes) based on blood pressure, use of antihypertensive drugs (ADs), plasma potassium and aldosterone concentrations.

Results

Fifty three patients (30 male / 23 female); aged 52.4 ± 11.2 years were studied. Mean postsurgical follow-up was 44.6 months (range 0-240). Complete clinical success and partial clinical success were achieved in 27 (50.9%) and 19 (35.8%) patients, respectively. In patients with postsurgical biochemical data, complete biochemical success and partial biochemical success were seen in 29 (70%) and 5 (12%), respectively. In univariate analysis, patients with complete clinical success were significantly younger than patients with partial or absent success (49.3 ± 10 vs 56.8 ± 10 vs 57.2 ± 8.7 years) ($P < 0.01$). Complete clinical success were more frequent in women (59.3% vs 26.3% vs 16.7%) ($P < 0.05$). Number of preoperative ADs, level of preoperative arterial blood pressure or serum potassium levels did not differ significantly between patients with different outcomes. Using binary logistic regression analysis only female sex was independently associated with complete success (OR 6.5 CI 95% 1.2-36.9, $P < 0.05$).

Conclusion

In our study, unilateral adrenalectomy for PA achieved complete or partial clinical and biochemical success in the majority of patients (86.7% and 82% respectively). Younger patients and female patients were more likely to have a favourable surgical outcome.

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P18

Intraoperative hypertensive crisis as a key symptom in a normotensive patient with primary aldosteronism – clinical case

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Primary aldosteronism is now recognized as the most frequent cause of secondary hypertension, accounting for 5–10% of the total cases of hypertension. Reportedly it is associated with a risk of cardiovascular events above and beyond hypertension development. Notwithstanding its high prevalence and serious complications, it is widely infradiagnosed. Hereby we present the case of a normotensive 50-year old female patient who was diagnosed of probable left

hypernephroma, but after anesthetic induction surgery was aborted due to a hypertensive crisis. The patient was referred to our Endocrinology Clinic in order to rule out pheochromocytoma. Anamnesis revealed recurrent hypokalemia (up to 2.6 mEq/L). Glucose, glomerular filtration rate, lipids and TSH were normal, K + 4.24 mEq/L, Aldosterone 59 ng/dL, PRA 0.7 ng/mL/h, ratio 84.3, Metanephrine 30 pg/mL, Normetanephrine 69 pg/mL, Cromogranine A 5.8 ng/mL. 24h ABPM showed normal mean values of BP and HR (118/76 mmHg, 77 bpm), with an isolated peak of 234/146 mmHg 81 bpm at 12:20. The abdominal CT report did not mention adrenal anomalies but on review the left adrenal image suggests nodular hyperplasia. A confirmatory captopril test did not elicit aldosterone suppresion (0' – > 120': 29.9 – > 21.7 ng/dL). The patient was treated with spironolactone 12.5 mg/day, she remains asymptomatic, with normokalemia, normotension and unsuppressed PRA. Pheochromocytoma was ruled out and a 4-cm left renal mass was successfully removed, the pathology diagnosis was oncocytoma, with negative extension. Surgical removal of the left adrenal was not considered. We conclude that normotensive primary aldosteronism is not harmless: it may cause hypertensive crisis and severe hypokaliemia. Evolution to resistant hypertension has also been reported. It must be considered as a diagnostic possibility in normotensive patients with unexplained hypokalemia.

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P19

Adrenal insufficiency during prednisolone treatment in patients with polymyalgia rheumatica or giant cell arteritis – prevalence and clinical approach

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Introduction
Prednisolone is standard treatment of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA), but many patients are reluctant to discontinue prednisolone treatment even after remission of the inflammatory conditions. Prednisolone-induced adrenal insufficiency can give manifest or latent symptoms, causing failure to taper and withdraw prednisolone. We therefore aimed to find the prevalence of adrenal insufficiency in prednisolone-treated patients with PMR/GCA.
Methods
A cross-sectional study of PMR/GCA patients treated with prednisolone for >6 months, currently 2.5–10 mg/day. Forty-seven patients (34 women) were included consecutively from the Rheumatology Outpatient Clinic. Adrenal function was evaluated by a fasting 250 μg Synacthen test in the morning following being prednisolone-free for 48-hours and oestrogen treatment free for P-weeks. P-cortisol concentrations were measured by Roche Elecsys® Cortisol II assay. Adrenal insufficiency was defined as P-cortisol <420 nmol/l 30 minutes after Synacthen injection (local assay specific cut-off). All patients with adrenal insufficiency were subsequently followed in a close rheumatologic-endocrine collaboration. Prednisolone tapering was based on PMR/GCA remission, Synacthen tests were performed regularly and the need for hydrocortisone stress doses/daily supplementations was adjusted accordingly.
Results
The 47 patients (mean age 73 years (SD 7.3)) were treated with prednisolone for median 23 months (range 5.4–139 months), with a mean current prednisolone dose of 5.3 mg/day (SD 2.0). Seven patients (15%, $CI_{95\%}$: 7.4–28%) had adrenal insufficiency. Current prednisolone dose correlated negatively with 30 min P-cortisol (−32 nmol/l/mg prednisolone, $CI_{95\%}$: −9.5–−55 nmol/l/mg, $P=0.0066$, $r=-0.39$), but adrenal insufficiency occurred across the entire prednisolone dose range (2.5–10 mg/day). There was no correlation between duration of treatment and 30 min P-cortisol ($P=0.24$, $r=-0.17$). ACTH levels were low within reference range (mean 4.6 pmol/l (SD 2.9)). Insufficient patients were informed of the condition and administration of necessary hydrocortisone stress doses. Subsequently, 5 patients were able to discontinue prednisolone treatment, 2 of whom recovered adrenal function, whereas 3 still need daily hydrocortisone replacement. Two patients were unable to stop prednisolone treatment due to PMR/GCA disease activity, and have occasionally needed excess steroid doses to overcome stress/adrenal crises.
Conclusion
Iatrogenic adrenal insufficiency occurred in 15% of low-dose prednisolone treated patients with PMR/GCA. In most patients prednisolone could be discontinued due to recovery of adrenal function or by switching to oral hydrocortisone. This illustrates the importance of a close collaboration between rheumatology and endocrinology.

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P20

Prevalance of primary aldosteronism in hypertensive patients: epidemiological data from a tertiary centre

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Introduction
Primary aldosteronism (PA) is the most common cause of endocrine hypertension. Its prevalence varies from 5-15%, which depends mainly on the cut-offs of the diagnostic tests.
Aim
To estimate the prevalence of PA in patients with different stages of hypertension based on a dynamic overnight diagnostic test.
Methods
One hundred ninety nine hypertensive patients were divided in 3 groups according to the stage of hypertension, as defined by the European Society of Hypertension. The three groups consisted of 77 patients at stage 1 [systolic blood pressure (SBP) 140 to 159mmHg and/or diastolic blood pressure (DBP) 90 to 100 mmHg], 65 patients at stage 2 (SBP 160 to 179 mmHg and/or DBP 100 to 109 mmHg and 57 patients at stage 3 (SBP ≥180 mmHg and/or DBP≥110 mmHg) respectively. Evaluation of PA was based on the combination of valsartan, captopril and dexamethasone suppression test (DCVT). Post DCVT aldosterone (ALD)>3 ng/dl and post-DCVT aldosterone to renin (ALD/REN) ratio>0.32 ng/dL/μU/mL were applied simultaneously to establish the diagnosis of PA.
Results
The diagnosis of PA using the DCVT test was confirmed in 60 of 199 patients giving a prevalence of 30,1%. The prevalence of PA according to the stage of hypertension was 27,2%(21/77) in patients of stage 1, 27,6%(18/65) in patients of stage 2, and 36,8%(21/57) in stage 3.
Conclusion
Using the DCVT a remarkably increased prevalence of PA (30,1%) was observed. The higher prevalence was observed in patients with severe hypertension (stage 3). Our data suggest that all hypertensive patients, especially those with severe hypertension should be tested for PA.

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P21

Renin: a possible novel marker for the efficacy of pharmacological treatment of primary aldosteronism

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Introduction
Primary aldosteronism (PA) treatment is either pharmacological with aldosterone receptor antagonists (MRAs) or surgical with the resection of the responsible adenoma. The efficacy of MRAs treatment is based on the normalization of blood pressure (BP) in relation to potassium levels. However, it remains unclear whether the stimulation of renin levels during treatment could serve as an additional marker of adequate MR blockade.
Aim
To investigate prospectively the effectiveness of MRAs on BP control in PA patients in correlation with renin levels.
Methods
Thirty eight patients diagnosed with PA, were treated with MRAs and were prospectively followed –up at regular intervals ranging from 3 to 12 months. All patients were instructed to have 2 consecutive BP measurements twice daily. Systolic (SBP) and diastolic (DBP) BP target were <135 and <85 mmHg respectively. Renin levels >7.8 μU/ml were considered as unsuppressed. In patients with raised BP (SBP or DBP) or renin levels <7.8 μU/ml MRAs dose was gradually increased.
Results
At the first follow up visit, 10 of 38 (26.3%) PA patients had normal SBP, DBP and unsuppressed renin levels. The initial MRAs dose ranged from 25 to 100 mg (mean 57.2 mg). Patients with unsuppressed renin levels had lower DBP compared to patients with suppressed renin levels (77.6 ± 7.3 mmHg vs 83.15 ± 8.7 mmHg, $P=0.04$). Patients with either elevated BP or suppressed renin levels received higher MRAs dose, which ranged from 50 to 200 mg (mean 104.5 mg). At the last follow-up 24 of 33 (72.7%) patients had normal BP and unsuppressed renin levels. Compared to the 1st follow-up, at the last follow up visit the PA patients improved SBP (136.9 ± 9.9 mmHg *vs* 127.8 ± 9.14 mmHg, $P<0.001$), DBP (80.2 ± 8.9 mmHg vs 75.6 ± 5.6 mmHg, $P=0.04$), raised renin (9.9 ± 8.1 μU/ml vs 16.3 ± 9.8 μU/ml, $P<0.001$) and potassium levels (4.2 ± 0.5 vs 4.4 ± 0.3 mEq/L, $P=0.024$). In addition, there was a negative correlation between mean MRAs doses and renin levels (r-0.42, P 0.014) at the last follow-up indicating that the higher MRA doses were needed in patients with supressed renin levels at the beginning of the study.
Conclusion
The targeted MRAs pharmacological treatment leads to an increase of renin levels and more effective BP control. According to our data, unsuppressed renin levels in combination with BP could be used as a novel marker of adequate MR blockade and can predict BP control.

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P22

Conn Syndrome Presented with Muscle Weakness

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Introduction
Aldosterone producing adenoma, called Conn syndrome, accounts for 10 percent of all hypertension cases. It should be remembered in patients with hypokalemia and hypertension however, this is not a rule. Conn syndrome can be presented with hypertension but normal potassium levels. Also, rarely it can be presented with hypokalemia but normal blood pressure as in our case.
Case report
34-year-old female patient complained about difficulty in walking and trips and falls without a cause. Assessment in neurology clinic revealed low potassium levels (2.6 meq/l) and normal sodium levels in the upper limit (141 meq/l). The patient is referred to our clinic. Abdominal ultrasound showed a 12×6 mm hypoechoic nodule in the right adrenal zone consistent with adrenal adenoma. She denied history of hypertension. Family history did not suggest Conn syndrome. Aldosterone levels were 257 pg/ml, plasma renin activity was 0.45 ng/ml/h, aldosterone/renin ratio was 57.1 after correction of serum potassium levels. Two controls gave similar results. Cortisol level was 15.61 μg/dl, ACTH level was 25.9 pg/ml. Cortisol levels were suppressed to <1.8 μg/dL after 1 mg dexamethasone suppression test. 24-hour urinary cortisol level was 37 μg/day (3.5–45). DHEAS level was 159 μg/dl (35–430). 24-h ambulatory blood pressure revealed a median blood pressure of 125/85 mm/Hg. Computed tomography for adrenal gland showed 16x10 mm lesion in right adrenal gland medial crus with a HU density of -2 which is consistent with adrenal adenoma. Left adrenal gland was normal. The patient was referred to surgery for aldosterone producing unilateral adrenal adenoma and undergone right adrenalectomy. The post-operative pathology was consistent with adenoma. The patient did not need potassium replacement after two days, as potassium levels were normal.
Discussion
Diuretic treatment, Bartter syndrome and persistent vomiting can cause hypokalemia without hypertension. However, primary hyperaldosteronism can also be presented with hypokalemia without hypertension. The differential diagnosis is easy as renin levels are low in Conn syndrome in contrast with others. Our patient had low renin and high aldosterone levels suggesting primary hyperaldosteronism. The pathology revealed adrenal adenoma. The maintenance of normal levels of potassium after surgery supported the diagnosis of Conn syndrome.

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P23

Large Oncocytic Adrenocortical Tumor with Uncertain Malignant Potential

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Introduction
Oncocytic tumor of adrenal gland was defined as a neoplasm composed exclusively or predominantly of oncocytes which are large and polygonal cells with eosinophilic cytoplasm because of abnormal accumulation of mithochondria. Oncocytic neoplasms of the adrenal cortex are extremely rare and are usually non-functioning, benign and incidentally detected.
Case
A 40-year old male patient, for whom a large mass in the adrenal gland was diagnosed incidentally on abdominal ultrasonography and MRI. The physical examination and laboratory tests were within normal limits. On the dynamic abdominal MRI imaging $9.5 \times 9.5 \times 10.5$ cm mass lesion was observed in the right surrenal region. 24-hour urine dopamine and VMA levels were slightly higher [VMA: 8.4 mg/24 h (0–6.6 mg/24 h) and Dopamine: 435.1 μg/24 h (<400 μg/24 h)]. Right -side adrenalectomy was applied to the patient. The histopathological diagnosis was reported by the Pathology Department as oncocytic adrenocortical tumor with uncertain malignant potential according to the Lin-Weiss-Bisceglia system (Large size and capsule invasion were detected). Immunohistochemistry (IHC) of the tumor cells were found positive for synaptophysin and negative for inhibin and chromogranin.
Conclusion
Adrenocortical oncocytoma is a very rare abnormality observed within the adrenal cortex. It is usually benign, non-functioning, large and diagnosed incidentally. Adrenal gland masses are best visualized on CT or MRI but still no definitive features can differentiate benign from malignant adrenal oncocytic neoplasm on imaging. Diagnosis is made histopathologically, so adrenalectomy is the mainstay of therapy and laparoscopy is now the most diffuse approach. According to Weiss criteria: the presence of one major criteria (high mitotic activity, atypical mitoses or venous invasion) indicating malignancy, one to four minor criteria (Large size, necrosis, capsular or sinusoidal invasion) indicating uncertain malignant potential (borderline) and the absence of criteria indicates a benign tumor. Our case was interesting because malignancy was clinically suspected before the operation, but the mass was found to be an oncocytic adrenocortical tumor with uncertain malignant potential through postoperative histologic assessment. Therefore, an oncocytic adrenocortical tumor with

uncertain malignant potential as in this case is considered to require long-term follow-up through clinical, hormonal, and imaging evaluation owing to its malignant potential.

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P24

Conjugated steroids could be a reserve stock for rapid conversion into free ones during stress

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Hypoglycaemia stimulation serves as a model of physiological function of adrenal action during the stress reaction. The study aimed to describe the differences of steroid response between hypoglycemia and various doses of Synacthen (as ACTH stimulation alone). The goal of the study was to investigate the physiology of adrenal response. Twenty four steroids were measured in plasma using gas chromatography - mass spectrometry after stimulation of 1 μg, 10 μg and 250 μg of Synacthen and after insulin administration in thirteen healthy subjects. Steroid conjugates significantly decreased in the first 20 minutes of stimulation by hypoglycemia, but did not change after 1 μg, 10 μg or 250 μg Synacthen administration. No differences between the secretion of adrenal androgens after stimulation by Synacthen or by hypoglycaemia were observed. The results suggest that the conjugated steroids in the circulation can serve as a reserve for rapid conversion into free steroids in the first minutes of the stress situation. The difference between hypoglycaemia and ACTH stimulation may be in concordance with the hypothesis that additional mechanism could be important in steroids reaction to the stress situation. This study was supported by the project MHCZ–DRO (Institute of Endocrinology – EU, 00023761) and grant 17-28692A.

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P25

Presence of comorbidities related to hypercortisolism in a case series on adrenal incidentaloma (AI)

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Introduction
The European Society of Endocrinology Clinical Practice Guideline defines follow-up recommendations for AI based on the 1 mg overnight dexamethasone suppression test and the presence of associated comorbidities. Follow-up is not recommended for AI presenting serum cortisol levels post dexamethasone $\leq$1.8 μg/dl neither those presenting serum cortisol levels post dexamethasone between 1.9–5 μg/dl (defined as 'possible autonomous cortisol secretion' –PACS-) in absence of comorbidities (such as arterial hypertension, diabetes, dyslipidemia, osteoporosis or obesity). On those patients presenting PACS and comorbidities the functional status should be reassessed after 6–12 months.
Objective
To evaluate hypercortisolism related comorbidities in a case series on AI patients attended in a specialized unit on diseases of the adrenal glands.
Patients and methods
We analyzed data from 237 AI diagnosed from February 2014 to June 2017. After excluding patients with hormonally active AI, malignancy or lesions not requiring follow-up (such as myelolipoma, adrenal hyperplasia or lesions $<$1 cm), 174 patients were catalogued as non-functioning AI. We compared the presence of comorbidities between patients presenting serum cortisol levels post dexamethasone $\leq$1.8 μg/dl (non-pathological –NP-) and those with PACS.
Results
From 237 patients, 78.1% were referred from: Urology Department 42, Gastroenterology Department 55, Internal Medicine Department 28 and Pneumology Department 11. 58.6% (102) were women and 41.1% (72) men. Mean age: 62.6$\pm$11.4 years (26–86). 80.5% (140) unilateral masses, most frequently on left adrenal gland (92/42). Masses on left side were bigger (2.43$\pm$1.15 cm, 1–8.2 cm) than those on right side (2.11$\pm$0.96 cm, 0.6–5.5 cm). From 174 non-functioning AI, 58.6% (113) presented NP and 34.5% (61) PPAC. Comorbidities: 58% (101) hypertension, 32.2% (56) diabetes, 33.9% (59) dyslipidemia and 31% (54) obesity. Mean BMI: 30.1$\pm$7.4 kg/m^2. Not statistically significant differences were found in prevalence of comorbidities between NP and PACS: arterial hypertension (52% vs 66%, $P=0.053$), diabetes (27.5% vs 38.9%, $P=0.133$), dyslipidemia (33.3% vs 34.7%, $P=0,849$), obesity (33.3% vs 27.8%, $P=0.288$).
Conclusions
A closer follow-up is recommended, in patients with AI, depending on presence of comorbidities, assuming those patients with comorbidities to have a higher risk of develop a marked hypercortisolism in the future. However, we have observed that comorbidities are present independently of serum cortisol levels post dexamethasone. Therefore, presence of comorbidities not seems not be attributable to the presence of subclinical hypercortisolism.

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P26

Increased levels of Interleukin-6 in patients with primary and secondary hypocortisolism: A case-control study

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Context
Hypocortisolism has been associated with increased cardiovascular risk (CVR) and mortality. Higher levels of certain inflammatory markers such as Interleukin-6 (IL6) in patients with adrenal insufficiency (AI) may partly explain the increase in CVR. Recent studies demonstrate an increased prevalence of cardiovascular disease (CVD) in patients with elevated IL-6 levels. Hypocortisolism is generally treated with glucocorticoid replacement therapy (GRT). Current GRT regiments fail to adequately mimic the physiological rhythm of endogenous cortisol leading to temporary supra- and infraphysiological levels of cortisol.
Objective
This study aims to evaluate serum levels of Interleukin-6 in patients with primary or secondary AI receiving hydrocortisone replacement therapy (HRT) in a clinical setting.
Material and methods
Ten patients (8 female, 2 male, mean age in years: 53,4, range 28–67) with either primary or secondary AI on HRT were analyzed for cortisol and interleukin-6 levels over the course of two days. Blood samples were drawn in 3-hour intervals. A cardiopulmonary exercise test was performed during the second day to induce stress. The results were compared to 5 healthy individuals. One female control patient was excluded because of tendinitis (Data not shown). Hydrocortisone was taken orally twice a day, once in the morning and once midday (mean dose: 28.75 mg, range 15–42.5). Exclusion criteria were coronary heart disease, inflammatory diseases, valvular heart disease and heart arrhythmia.
Results
A total of 10 AI patients and 4 healthy controls were included in this study. Both groups were comparable with respect to sex and age. Compared to healthy controls, patients with primary or secondary AI showed higher levels of IL-6 over the course of two days (mean IL-6 AI group: 8.1 μg/dl (range: 4.25–14.15) vs healthy controls 5.1 μg/dl (range: 2.54–8.8); $P=0.0970$). At midnight of the first day AI patients showed significantly higher levels of IL-6 compared to healthy controls (mean IL-6 at 2400 h: 7.56 μg/dl vs 3.15 μg, $P=0.0375$) while midnight serum cortisol levels were higher in healthy controls (mean cortisol at 2400 h: 2.65 μg/dl vs 1.37 μg; $P=0.25$).
Conclusion
Our study indicates that hypocortisolism in AI may lead to a compensatory secretion of IL-6, therefore increasing the risk of cardiovascular disease and ultimately mortality. Retarded hydrocortisone preparations with a dual-release may deliver a new therapy option in avoiding increased levels of IL-6 in AI patients.

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P27

A new *ARMC5* mutation responsible for primary bilateral macronodular adrenal hyperplasia

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Introduction
Primary bilateral macronodular adrenal hyperplasia (PBMAH) is a rare cause (<2 percent) of endogenous Cushing's syndrome, usually characterized by enlarged adrenal glands containing multiple functioning nonpigmented macronodules. PBMAH was thought to be sporadic, but recently a genetic component has been described. Specifically, inactivating mutations in *ARMC5* (Armadillo-repeat containing 5), a suppressor gene, have been found in many familial cases of PBMAH, and are thought to be the most common genetic cause of this disorder. We report a case of PBMAH with a not previously reported *ARMC5* mutation.
Case report
A 65-year-old man was referred for the study of hypogonadotropic hypogonadism. Blood test revealed an elevated 0800 h cortisol of 27.5 μg/dl. 24-hour urinary free cortisol (UFC) level was high (201.7 μg/24 h) and after 1mg dexamethasone overnight his baseline cortisol failed to suppress (21.5 μg/dl). Baseline ACTH was undetectable (<1 pg/ml). The computed tomography (CT) scan revealed multiple large nodules throughout both adrenal glands consistent with benign cortical adenomas (right gland 63×31 mm and left gland 41×39 mm). Functional study was completed without showing other disorders. Screening for aberrant adrenal receptors showed a total response to terlipressin (+163.98%) and a partial response to upright posture (+39.57%). A molecular analysis by sequencing *ARMC5* gene identified a heterozygous splicing mutation, c.476-2A>T (NM_0011005247.1), not previously reported. The mutation will most likely lead to an in-frame loss of exon 2 from the transcript. Therefore, we confirmed the diagnosis of PBMAH type 2 caused by a mutation in the *ARMC5* gene. Genetic testing of the patient's son did not show the mutation. Adrenalectomy of the largest gland was performed, achieving normal UFC levels and restitution of the gonadal function.
Conclusion
PBMAH is an underrecognized genetic condition that can lead to Cushing's syndrome with the consequent increase of the morbimortality. Identifying a pathogenic mutation of *ARMC5* and performing a genetic screening for predisposition to PBMAH could lead to earlier diagnosis and prevention of long-term complications of Cushing's syndrome.

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P28

Abstract withdrawn.

P29

Secondary adrenal insufficiency – is not this diagnosis often made too hasty?

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Introduction
Isolated corticotropic insufficiency of hypophysis with consecutive secondary adrenal insufficiency is a very rare disease. Literature notes difficulties in proper recognition and necessity of differential diagnosis, including among others chronic fatigue syndrome. In recent years, in Poland we observe more and more frequently setting this diagnosis – only on the basis of low ACTH an cortisol concentrations, despite of proper stimulation with 250 μg$^{1\text{-}24}$ACTH. As a result patients are treated with glucocorticoids, which, even in substitution doses increase risk of metabolic syndrome development.
Aim of the study
Our aim was to validate a diagnosis of secondary adrenal insufficiency in patient on prolonged treatment with Hydrocortisone.
Method
In 77 consecutive patients with Hydrocortisone treatment (6–24 months) referred to Clinic with diagnosis of secondary adrenal insufficiency (despite of proper stimulation with 250 μg 1-24 ACTH.), the 1mcg $^{1\text{-}24}$ACTH stimulation (proper cortisol concentration >18 μg/dl) then the Metyrapone tests (proper deoxycortisol concentration >7.5 μg/dl) were performed. Tests were done after 2-days cessation in Hydrocortisone medication.
Results
Only in 13 patients (17%) low-dose ACTH test confirmed diagnosis of adrenal insufficiency, and in 10 of them also after-metyrapone deoxycortisol concentrations were too low. In 22 (28%) persons with proper stimulation after 1 and 250 μg $^{1\text{-}24}$ACTH insufficient deoxycortisol increase after Metyrapone was stated. In the others 42 (55%) patients results of the both test were correct. In this group we were able to successfully stop Hydrocortisone treatment.
Conclusions
1. In significant percentage of the cases recognized as secondary adrenal insufficiency only on the basis of random cortisol and ACTH measurements the diagnosis can be false-positive.
2. In patients with isolated corticotropin deficiency classic stimulation test with $^{1\text{-}24}$ ACTH can give false-negative results and should be followed by low dose $^{1\text{-}24}$ACTH test and Metyrapone test.

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P30

Assessing the new Primary Aldosteronism guidelines recommendation to omit confirmatory testing in selected patients – severity of hypokalaemia may be included

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Background
Patients with an elevated aldosterone renin ratio (ARR) should proceed for a confirmatory test to diagnose primary aldosteronism (PA) before undergoing further investigations such as CT imaging and adrenal venous sampling. The recent 2016 clinical guidelines have included a new recommendation: that in the setting of spontaneous hypokalaemia, undetectable plasma renin, and plasma aldosterone concentration (PAC) >20 ng/dl, patients may not require further confirmatory testing. We retrospectively evaluated the utility of this, in all patients diagnosed in our tertiary unit over the last 17 years.
Methods
All patients who had undergone both a screening test (ARR) and salt loading tests (SLT) in Changi General Hospital, Singapore, from 2001 to 2017 were included. Hypokalaemia was taken as $K < 3.5$ mmol/l (laboratory reference 3.5–5.0 mmol/l). Positive salt loading test was taken as post-salt loading PAC > 10 ng/dl. We assessed the sensitivity and specificity of the above criteria in predicting a positive salt loading test.
Results
90 patients, mean age 53.3±12.7 years, 51 (56.6%) males, underwent both screening ARR and confirmatory SLT from 2001–2017. 65.5% (59 of 90) patients had a positive SLT. 12.2% (11 of 90) patients fulfilled the above criteria of spontaneous hypokalaemia, undetectable plasma renin, and PAC > 20 ng/dl. Of these 11 patients, 10 (90.9%) had a positive SLT. The above criteria had a specificity of 96.8% and sensitivity of 16.9% in predicting salt loading positivity. The positive predictive value was 90.9%. In the 1 patient who fulfilled the new criteria but had a negative SLT, the lowest potassium level was 3.4 on several occasions (without other contributory factors), with baseline aldosterone 21.8 ng/dl, renin undetectable, and post-SLT aldosterone 3.46 ng/dl. The remaining 10 patients all had a potassium level of ≤3.0 mmol/l.
Conclusion
The new additional criteria (spontaneous hypokalaemia, undetectable plasma renin, and PAC >20 ng/dl) was demonstrated to be highly specific for positive salt loading test results, which would have benefitted 11% of our patients who would not have needed to undergo a confirmatory test. However, one patient with mild spontaneous hypokalaemia had a negative confirmatory test. Hence, the severity of spontaneous hypokalaemia should also be taken into account, and our

data suggest that a potassium level of ≤3.0 may be included in the criteria, to help accurately identify patients who do not need further confirmatory tests.

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P31

Addison's disease due to adrenal tuberculosis; A case report

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During the past decades, incidence of adrenal tuberculosis has been greatly decreased due to the introduction of antituberculosis drugs. It is reported that primary adrenal insufficiency (PAI) results from adrenal tuberculosis accounting for only 15%–20% patients in developed countries. Adrenal tuberculosis is the major cause of chronic PAI especially in developing countries. A 53 year old man presented with a 3 month history of generalized weakness, anorexia, weight loss and dizziness. His past medical history was unremarkable. Physical examination showed hypotension (85/60 mmHg) and nevuses in many parts of body. Laboratory evaluation was significant for hyponatremia, hyperkalemia and mildly increased creatinin and C-reactive protein values. Cortisol level was 3.8 mcg/dl with an ACTH level of 662 pcg/ml which was consistent with the diagnosis of primary adrenal insufficiency. A contrast enhanced abdomen magnetic resonance imaging (MRI) showed a mass,measuring 20×15 mm in the medial limb of right adrenal gland and a mass measuring 22×25 mm in the lateral limb of right adrenal gland and masses measuring 20×15 mm and 20×14 mm at the level of the left adrenal gland corpus. The masses showed heterogenity and necrotic components after contrast. Thorax CT showed sequelae findigs on apex of the right lung probably due to tuberculosis. Due to the possibility of adrenal malignancy or metastasis 18F-fluorodeoxyglucose positron emission tomography (FDG PET) CT scan was additionally performed. FDG PET-CT scan showed uptake only in the adrenal glands on both sides. Tru-cut biopsy was performed on the right adrenal gland. Cytology revealed necrotising granulomatous reaction supporting tuberculosis. A diagnosis of adrenal insufficiency secondary to tuberculosis was made, and treatment with hydrocortisone, fludrocortisone for adrenal insufficiency and antitubercular therapy was started. After 2 months the masses were not seen on the left adrenal gland, size of the masses on the right adrenal gland was decreased. He is still using hydrocortisone, fludrocortisone and antitubercular therapy.

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P32

How can cortisol-normalized adrenal venous sampling miss some Conn's adenoma

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Introduction
In patients with primary aldosteronism (PA) international consensus claim that adrenal venous sampling (AVS) performs better than CT scan in determining lateralization of aldosterone secretion. The SPARTACUS study has however reported similar performances for lateralization by CT scan and AVS in patients with PA and a unilateral adrenal mass. The standard procedure for AVS uses cortisol values to validate the selectivity of catheterization and to normalize the aldosterone values before calculating lateralization index (LI). In this study we show that normalisation by cortisol in AVS can induce a wrong lateralization of aldosterone secretion in some patients with PA.
Objective
To analyze discordances between lateralization predicted by CT scan or by AVS in patients with PA and a unilateral adrenal mass.
Methods
Monocentric retrospective analysis of data of 33 selective AVS in patients with PA and a unilateral adrenal mass. AVS was performed simultaneously on both adrenal veins (AV) without stimulation and normalized with cortisol but also epinephrine. LI>4 was considered significant. Immunohistochemical analysis of CYP11B1, CYP11B2 and CYP17 was performed in the adrenal adenoma of one patient.
Results
One patient with severe hypertension and hypokalemia showed PA, no hypercortisolism and a 2 cm right adrenal mass. AVS was selective in both AV and cortisol-normalized AVS showed right/left LI = 0.8, ruling out lateralization, despite higher absolute values of aldosterone, but also cortisol, in the right AV. By contrast epinephrine-normalized AVS showed right/left LI = 6.25. The patient showed poor tolerance of anti-aldosterone treatment and eventually underwent right adrenalectomy, resulting in normalization of BP and remission of PA. Immunochemical analysis of the right adrenal adenoma showed expression of CYP11B2 but also CYP11B1 and CYP17, which allows to secrete both aldosterone and cortisol. Analysis of the 32 other patients identified five discordances between cortisol-normalized AVS lateralization and epinephrine-normalized AVS, with 2/5 patients showing concordance in epinephrine-normalized AVS and CT scan.
Conclusion
Cortisol-normalized AVS can fail to detect lateralization of aldosterone secretion by some Conn's adenoma which secrete not only aldosterone but also cortisol. These adenoma are not necessarily detectable pre operatively as they may show a normal 1mg Dexamethasone test. They have recently been reported to be frequent and may represent one explanation for the good performances of CT scan in the SPARTACUS study. We propose that AVS aldosterone values be normalized on epinephrine or on any product secreted by the adrenal gland, but not by the adenoma.

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P33

ACTH stimulation test for study of primary aldosteronism

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Introduction
Primary aldosteronism (PA) is the principal cause of arterial hypertension potentially treatable. The diagnosis is dependent of tests to identify patients who will benefit most with surgical treatment. ACTH stimulation test (AST) has been described as a useful confirmatory test, potentially identifying bilateral disease in patients without adrenal tumors.
Aim
Evaluate the AST in patients with hypertension and positive screening test for PA, which performed saline infusion test (SIT).
Methods
Retrospective observational study which included 12 patients that performed SIT and AST as confirmatory tests for PA, from May to October of 2017. IST consisted in infusion of 2,000 ml of 0.9% saline over 4 h. Was considered positive if plasmatic aldosterone concentration (PAC) ≥ 100 pg/ml, negative < 50 pg/ml and indeterminate between ≥50 pg/ml and <100 pg/ml. AST consisted in intravenous injection of 250 μg of tetracosactide acetate with measurements of PAC and plasmatic cortisol at every 30′ for 2 h and was considered positive if PACmax/cortisol ≥8.5. Bilateral disease was considered if PACmax/cortisol <18.2 and no adrenal tumor on CT scan.
Results
Median age was 54 years and 75% were female. Six patients had adrenal tumor on CT scan, four without tumor and two were unknown. Of patients with adrenal tumor, 1/3 were at right, 1/3 at left and 1/3 bilateral. All patients were treated with antihypertensive agents except 1. The median PACmax/cortisol was 10.5 (IQR 8.56–15.52). 8 reached PACmax at 60′, 3 at 30′ and 1 at 90′. Three patients had positive SIT and also positive AST (PACmax/cortisol = 12.18–106.32). 2 patients had negative SIT and also negative result at AST (PACmax/cortisol = 5.04–8.49). Of seven patients with indeterminate result at SIT, the AST was negative in only 1 (PACmax/Cortisol = 7.4). Patients with positive AST presented higher PAC at SIT (P = 0.013) and lower K+ levels (P = 0.02). Of patients without adrenal tumor, one had diagnosis excluded in both tests and the others presented PACmax/cortisol <18.2, consistent with bilateral PA.

Conclusion
This data show that results between SIT and AST in positive and negative cases were consistent. In cases where SIT was indeterminate, AST may be useful as a confirmatory test of PA. Patients without adrenal tumor presented an AST result consistent with bilateral PA, reducing the need for adrenal catheterization in this context. However, a larger sample is required for the validation of AST as a diagnostic test, as well as for assessing the benefits of PA treatment in patients with positive AST.

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P34

Value of 131I-Norcholesterol scintigraphy in the evaluation of primary hyperaldosteronism

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Background
131I-norcholesterol scintigraphy (INCS) is currently not considered a main confirmatory and localizing study in primary aldosteronism (PA), however few recent data is available. On the other hand, adrenal venous sampling (AVS) is technically difficult, and may also lead to erroneuos diagnosis.
Aim
To describe the performance of INCS, done under dexamethasone (DXM) supression, in daily practice.
Patients and methods
Retrospective study of the 36 INCS-DXM performed from 1/2011 to 12/2017 at our centre, that were requested in cases of PA to decide surgery. DXM 4 mg/day was administered from day -7 to the fourth day of detection. Images were adquired at 24, 48 h, and late images, off of DXM, on 5th/7th day.
Results
20 (55.56%) were male, mean age was 58.6 ± 13.7 years. INCS was negative in 22 patients (61,1%), 11 cases (30.5%) showed unilateral autonomous nodular uptake (UANU). In three cases the report was glandular assymetry (2) or bilateral hyperplastic behaviour (1), and were treated conservatively. After committee decision nine patients (25%) were operated on (laparoscopic adrenalectomy). Eight of them had congruent UANU with ipsilateral adenoma by CT, and blood preassure ressolved completely (7) or improved (1). Only one patient with negative INCS was adrenalectomized and cured of Conn's adenoma, standing for the only false negative result (11%). 3 cases with UANU were not operated on (one had serious comorbidities, one showed contralateral adenoma on CT but refused AVS, one mild case preferred medical treatment). The sensitivity of INCS among surgical confirmed cases was 88.8%. In this series, INCS-UANU was associated to adrenalectomy (P 0.01). Hypokaliemia was associated to INCS positivity ($P<0.016$) and to surgery ($P<0.001$). Supressed renin (<0.5 ng/ml/h) did correlate to INCS positivity (P 0.001) and adrenalectomy (P 0.045), however neither plasmatic aldosterone nor aldosterone/renin ratio >30 did. Adenoma's mean size was not related to INCS result (P 0.7) or to surgical management (1.74 ± 1.2 vs 1.72 ± 0.45 mm) (P 0.9). Neither the INCS result nor the treatment were associated to gender, however, the mean age of the operated was significantly younger (47.4 ± 15.1 vs 62.2 ± 11.6) (P 0.022).
Conclusions
The usefulness of INCS in the work up of primary hyperaldosteronism due to Conn's adenoma is confirmed, with a sensitivity of 88%. INCS is a minimally-invasive functional imaging that should be taken into account before performing AVS.

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P35

A four months infant survival case of waterhouse–friderichsen syndrome

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Introduction
The Waterhouse–Friderichsen syndrome is a fulminating infection, often leading to mortality in a matter of hours by producing acute adrenal insufficiency (adrenal hemorrhage) at a time when their response is crucial to address acute stress.
Case report
We present the case of a 4 months boy with high fever 40 °C, vomiting, diarrhea, lethargy, maculopapular rash followed by petechiae and purpura. Biological tests revealed important leukocytosis and thrombocytopenia. Gram staining of cerebrospinal fluid pointed out gram-negative diplococci and latex agglutination testing was positive for type B meningococcal infection. With Glasgow Coma Scale of four the patient was admitted in the Intensive Care Unit and the evolution was positive with biological and clinical resolution after 14 days. ACTH 209 pg/ml (0–46 pg/ml) and cortisol 4.3 μg/dl (5–25 μg/dl) outlined the adrenal insufficiency.
Conclusion
Despite the high mortality rate (55–60%) our patient survived due to fast and accurate diagnosis. The incidence of Waterhouse–Friderichsen syndrome in Romania is 5.88/year/100,000 population aged 0–2 years, more frequent in countryside area males with poor socio-economically status as our patient's case.
Key words: Waterhouse–Friderichsen syndrome, meningococcaemia, infant.

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P36

Hypoaldosteronism induced by trimethroprim: hyponatremia is frequent

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Introduction
Hypoaldosteronism is characterized by the development of hyperkalemia, but can also induce hypovolemic hyponatremia. Trimethroprim can cause hypoaldosteronism through mineralocorticoid resistance. That hypoaldosteronism can induce hyponatremia in absence of Addison's disease has been questioned. We studied the electrolyte disturbances found following initiation of trimetroprim therapy.
Material and methods
Retrospective, analytical. Laboratory tests of 100 consecutive patients receiving trimethroprim in 2017 in a tertiary hospital, after excluding patients with baseline (B) hyperkalemia or hyponatremia. Electrolytes mmol/l. Hyponatremia: serum sodium (SNa) <135; hyperkalemia: serum potassium (SK) >5. Baseline electrolytes were compared to maximum SK and nadir SNa after starting trimethroprim. Results in mean (S.D.), or median (interquartile range).
Results
Age: 71.55 (13.55), 51% males. Bcreatinine: 0.77 mg/dl (0.56–1.13). BSK: 4.14 (0.58). SK rose 0.65 (0.74) ($P<0.0001$). SK increment was >0.2 in 76%: 0.92 (0.6) ($P<0.0001$). 35% patients developed hyperkalemia. 10%: SK >5.5. BSK was higher in patients developing hyperkalemia: 4.32 (0.58), than in those maintaining normokalemia: 4.04 (0.6) ($P=0.018$). BSNa:138 (2.9) descended to 135.6 (4.5) ($P<0.0001$). 46% developed hyponatremia: SNa 132.3 (3.8), 6/46 without a SK rise. BSNa in patients presenting hyponatremia was lower: 137.8 (2.8) than in those not: 139.6 (2.76) ($P=0.002$). 25/35 patients presenting hyperkalemia developed hyponatremia. In these, creatinine rose from 0.82 mg/dl (0.6–1.28) to 0.99 (0.59–1.67) ($P=0.038$). There was a weak correlation between SK elevation and SNa descent: $r=-0,26$ ($P=0.034$). Days of treatment (DOT): 7.5 (5–11.5), with weak positive correlation between DOT and SK increment ($r=0.31$) ($P=0.01$), negative correlation for SNa ($r=-0.31$) ($P=0.01$). Weak positive correlation between trimethroprim-cumulative dose and SK changes ($r=0.23$) ($P=0.04$), negative for SNa ($r=-0.27$) ($P=0.01$). Blood gas bicarbonate descended <23 mEq/l in 5/28. No patient had cortisolemia determined. There was no significant difference in SK or SNa changes in 64/100 patients receiving pharmacological doses of prednisone/methyl-prednisolone versus those not. K rise and-or Na descent were not significantly influenced by heparin, ACE inhibitors, ARBs, NSAIDS, beta-blockers, or furosemide therapy, gender, age, the presence of Diabetes Mellitus, urinary tract infection or obstructive uropathy.
Conclusions
Trimethroprim-induced hypoaldosteronism is frequent, potentially causing hyperkalmia and, more often in our series, hyponatremia. In patients presenting both, creatinine levels rose, suggesting hypovolemia onset. Trimethroprim, inducing mineralocorticoid resistance, could also be unmasking subclinical Addison's Disease. However, the fact that steroid medication in 64% of patients affected neither K rise nor Na descent suggests that these electrolye disturbances should not be attributed to Addison's Disease.

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P37

Utility of adrenal venous sampling for the differential diagnosis of primary hyperaldosternoism subtypes

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Introduction

In patients with primary hyperaldosteronism, distinguishing between unilateral and bilateral adrenal hypersecretion is critical in assessing treatment options. Adrenal venous sampling (AVS) has been advocated by some to be the gold standard for localization of the responsible lesion however is invasive, technically challenging, and difficult to interpret. Adrenal computed tomographic scanning (TC) is mandatory before AVS but more studies are warranted to identify its sensitivity and specificity for subtype differentiation.

Objectives

To study the utility of the MVS in the diagnosis of subtype of PAH and its concordance with the CT.

Methods

A retrospective study of 51 patients with a biochemical diagnosis of primary hyperaldosteronism who all underwent CT scan and AVS before and after ACTH stimulation. The aldosterone-to-cortisol ratio (AC) was computed for each sample to correct for varying capture and dilution of adrenal venous effluent. Patients that demonstrated unilateral hypersecretion of aldosterone were referred for an adrenalectomy. Diagnosis of a unilateral hyperfunctioning adrenal gland was made if the AC ratio on one side was at least four times greater than on the contralateral side and the peripheral samples. An AC ratio that was lower than periphery on the unaffected side (<0.5) especially after stimulation suggested a suppressed gland and therefore a unilateral hyperfunctioning gland on the contralateral side. Diagnosis of bilateral hyperplasia was made if the AC ratio on both sides was elevated and the response to stimulation was similar with no gradient observed between the two sites.

Results

Of 26 patients that had a unilateral abnormality on CT scan, four patients lateralized to the contralateral side by AVS, and seven patients had AVS consistent with bilateral hyperplasia. Therefore, 11 patients (21%) would have had either an unnecessary adrenalectomy or adrenalectomy of the nonfunctioning adrenal gland if AVS was not performed. In 12 patients that showed bilateral disease on CT scan, AVS lateralized to one side in eight patients and was concordant with the CT scan in 4 patients. In 13 patients that had no abnormality on CT scan, seven lateralized with AVS. 15 patiens (29.5%) would have been deprived of a curative suprarenalectomy. Of the group of 51 patients, 25 patients (50%) would have been inappropriately managed based on CT scan findings alone.

Conclusions

Because 50% of patients would have been inappropriately managed based on CT scan findings, patients with biochemical evidence of primary hyperaldosteronism and considering adrenalectomy should have AVS.

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P38

Non-classic congenital adrenal hyperplasia clinics characteristics and treatment response cohort study

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Introduction

Non-classic congenital adrenal hyperplasia (NCCAH) is an autosomal recessive disorder, that affects adrenal steroidogenesis, and it is characterized by an enzymatic defect in corticosteroids biosynthesis. NCCAH diagnosis is based on the determination of 17a-hydroxiprogesterone (17a-OHP) basal levels, and levels after stimulation with adrenocorticotropic hormone (ACTH), and it is confirmed with molecular testing. Treatment is still controversial, and it must be individualized because there are not steroid regimens to treat patients with NCCAH.

Objective

This study aims to describe the clinical characteristics, and compares the treatment response in patients with NCCAH that went to endocrinology consultation in a high complexity health institution in Cali, Colombia.

Methods

The study was conducted in a cohort of patients that registered at hospital since January 2006 to December 2016, with one year follow up, collecting 38 patients with NCCAH, diagnosed by clinical suspicion and confirmed with ACTH test. We describe the population and measure the response of 17-OH progesterone, testosterone and dehydroepiandrosterone sulfate (DHEA-S), at 6 and 12 months after treatment with dexamethasone and ethinyl estradiol plus cyproterone acetate. A $P<0,05$ was considered to establish statistically significant differences.

Results

Of the 38 patients included as total sample, the average age of participants was 25 years (s.d. 8, 9 years), average BMI was 28.3 kg/cm (s.d. 4.3). In the variance analysis we found for 17-OH progesterone levels a median of 15.9 ng/ml (IQR 12–19) at baseline, 1.65 ng/ml (IQR 1.4–3.3) at 6 months and 1.1 ng/ml (IQR 0.73–1.7) at 12 months. Total testosterone levels had a median of 103 ng/dl (IQR 79–138) at baseline, 62 ng/dl (IQR 50–77) at 6 months and 48 ng/dl (IQR 32–59) at 12 months. DHEA-S levels had a median of 452 µg/dl (IQR 370–536) at baseline, 209 µg/dl (IQR 154–306) at 6 months and 144 µg/dl (IQR 105–208) at 12 months, showing a decrease in hormone levels after the beginning of treatment, all statistically significant ($P<0.05$). Testosterone levels were influenced by BMI ($P=0.04$).

Conclusion

Pharmacologic intervention with dexamethasone at different doses, added to ethinyl estradiol plus cyproterone acetate, showed favorable results, by decreasing the serum levels of the measured hormones, during all the follow up period with statistically significant difference. Additionally, it was found that the testosterone values are influenced by BMI, without finding any difference in the other variables.

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A rare incidentaloma: adrenal schwannoma

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Introduction

Adrenal schwannoma is an extremely uncommon cause of incidentaloma. It originates from neural sheath Schwann cells of the adrenal gland. Herein, we report a case of left adrenal schwannoma that could not be diagnosed preoperatively.

Case report

A 53 years old female morbid obese (BMI: 66.68 kg/m^2) patient was referred to endocrinology policlinic because of 5 cm left adrenal mass detected on abdominal screening while preparing patient to bariatric surgery. In patients medical history she has been diagnosed with obesity, hypertension and type 2 diabetes mellitus for 8 years. She was using oral antidiabetics, zofenopril and alpha receptor antogonist for hypertension. We ceased zofenopril treatment before testing function of adrenal mass. Plasma renin activity, serum potassium, aldosterone, cortisol (11.2 µg/dl, normal range: 6.2–19.4), dopamin, and 24 h urine fractionated metanephrines levels were in normal ranges, but in 1 mg dexametasone suppression test patients' serum cortisol level was 2.23 µg/dl. We decided to left laparoscopic adrenalectomy because of mass size and subclinical Cushing syndrome. In histopathological examination of *material* obtained by surgical *excision* reported 4.5 cm adrenocortical adenoma contained myelolipomatous metaplasia and 3 mm adrenal schwannoma. After surgery, we found a suppressed cortisol level (0.58 µg/dl) with 1 mg dexametasone suppression test.

Discussion

A schwannoma in the adrenal gland is very rare and typically originates from the adrenal medulla. The low incidence and asymptomatic nature of the disease with no hormonal production make a definitive diagnosis of schwannoma in the adrenal region difficult leading to misinterpretation of the mass as an adrenal adenoma or cancer.

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P40

Cardiovascular risk in patient with incidentally detected adrenal masses – associated with metabolic syndrome and hypercortcism

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Background
Adrenal incidentalomas (AI) represent incidentaly discovered adrenal mases, without simptoms or signs suggestive of adrenal pathology, at the time of visualization. It is well-known that overt or subclinical hypercorticism, as well as metabolic syndrome (MetS) harbour increased CV risk.There is still persisting debate on eventual cause-effect relationship of AI with metabolic syndrome MetS or probability of simply more frequent occurance of AI among these patients.
Objective
The aim of this investigation was to assess the 10-year CV risk in patients with AI, as well as the impact of the presence of MetS or hypercorticism on CV risk in thise patients.
Methods
Study included 64 patients with AI, 49 patients with MetS and without adrenal pathology and 23 patients with proven Cushing's syndrome. For the identification of MetS, the International Diabetes Federation (IDF) definition was used. The patients were diagnosed with subclinical hypercorticism (SC) based on the presence of laboratory abnormalities of the hypothalamic-pituitary-adrenal axis, without clinical signs of Cushing's syndrome and hypercortisolism. Ten-year CV risk was assessed for every subject using the Framinghamskog score system.
Results
Prevalence of MetS among patients with AI was high (76.6%) and did not differ significantly from its prevalence among patients with proven Cushing's syndrome (69.6%). Presence of MetS significantly affected estimated 10-year CV risk in patients with AI (MetS+: 24.39% vs MetS-: 14.58%, $P<0.05$), while such impact of SC was not observed (SC+: 23.63% vs 21.23%, ns) in these patients. Among parameters that were tested, the most important predictors of 10-year CV risk, among patients with AI, as well as in those with MetS and those with proven Cushing's syndrome, proved to be age, high density cholesterol and fasting plasma glucose.
Conclusions
High prevalence of MetS in patients with AI and its influence on amplification of CV risk, indicate the necessity of inclusion of screening on its components, beside usual screening of adrenal function, in regular follow-up of these patients. This approach could allow appropriate and more agresive treatment aiming at the prevention of adverse cardiovascular events.
Key words: adrenal incidentaloma, metabolic syndrome, subclinical hypercorticism, cardiovascular risk

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P41

Outcomes of patients undergoing surgery for primary aldosteronism based on adrenal venous sampling and/or radiological lateralisation indicate a role for both modalities in case selection

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Background
Adrenal venous sampling (AVS) is considered the gold standard for lateralisation of aldosterone production in patients with primary aldosteronism (PA). However, in some patients AVS is not technically successful and management may depend on radiological findings.
Aim
To determine 1) the success rate of AVS and 2) the outcomes after surgery related to the lateralisation modality.
Method
156 patients were included who presented 2007–2017 with a confirmed diagnosis of PA. Success of AVS was defined by the Endocrine Society 2016. Outcome criteria were 1) systolic blood pressure <140/90 mmHg 2) serum potassium <3.8 mmol/l 3) serum aldosterone <140 pmol/l 4) 0–1 anti-hypertensives post-op or two medications fewer than pre-op. The cohort was divided into approximate tertiles based on the year of referral: 2007–2013, 2014–15 and 2016–17
Results
Success rate of AVS increased from 30% (2007–13) to 77% (2016–17) ($P<0.001$). 26 (16%) were of young age, had a solitary lesion and were referred for surgery (group I). 94 underwent AVS, of whom 39 (41%) had a unilateral source (group IIA); 12 (13%) had bilateral secretion (group IIB) and 43 (45%) had non-diagnostic AVS (group IIC). 41 of the total were treated medically (group III). 148/156 underwent imaging: unilateral adenoma (95, 64%) dominant nodule (28, 18%) or no lesion (25, 16%). 69 patients proceeded to surgery: 23/26 (88%) from group I, 28/39 (71%) of patients from group IIA and 18/43 (43%) from group IIC. Post-operatively: 57% of patients had BP<140 (30% preop) $P=<0.01$; 71% serum potassium <3.8 (14% preop) $P=<0.01$; serum aldosterone fell from 1050 to 254 pmol/l ($P<0.01$), the number of anti-hypertensives decreased to from 2.6 to 0.9 post-operatively. Interestingly, there were no statistically significant differences between groups I, IIA and IIC in meeting successful outcome as defined by the ES Guidelines: these were met in 50% of those in group I, 41% of group IIA and 53% of those in IIC.
Conclusions
Increased experience and technical refinement led to an significant increase in success rates of AVS. Patients treated with surgery had good clinical outcomes. However, we found equivalent success rates between those patients with lateralisation from AVS or radiology. This suggests that in patients where AVS is inconclusive or non-diagnostic, a proportion of patients will still improve with surgery.

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The response of C_{19}- Δ^5-steroids to ACTH stimulation

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The adrenal androgens dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, 5-androstenediol and 11β-hydroxy-androstenedione have a wide spectrum of important physiological effects. Aim of our study was to find differences in reaction of the C19 Δ5-steroids between healthy women and patients with adrenal insufficiency in various doses of Synacthen (1 ug, 10 ug and 250 ug). Our study involved seven healthy women and six premenopausal females (BMI and age matched) with primary adrenal insufficiency. C19 Δ5-steroids and their polar conjugates were measured in plasma using gas chromatography-mass spectrometry. Both free and conjugated steroids in patients did not show significant increase, in contrast to the levels in healthy controls (in all doses of Synacthen). Except for free DHEA and 7β-hydroxylated dehydroepinadrosterone derivatives, even the basal levels significantly differed between the patients with adrenal insufficiency and healthy controls. Changes of steroids conjugates during the ACTH test were insignificant in healthy controls. DHEA and its hydroxylated metabolites could be valuable markers of the integrity of the HPA axis. The art of stimulation of 7- and 16-hydroxylated metabolites of DHEA can help our understanding of the formation sequence of these compounds.

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P43

Non-classical form of congenital adrenal hyperplasia in patients with bilateral incidentalomas – hormonal and genetic analysis

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Incidentalomas of adrenal glands are found in approximately 0.4–4.4% of abdominal CT-scan examinations and some of them can be caused by congenital adrenal hyperplasia (CAH). Bilateral masses can be detected in 10–15% of cases. CAH is one of the most common autosomal recessively inherited disorders. Non-classical form of congenital adrenal hyperplasia (NCCAH), is the milder form of the 21-hydroxylase deficiency, with the estimated incidence of 1:1000 worldwide.

Aim
The aim of the study was to estimate the prevalence of NCCAH in patients with incidentally discovered bilateral adrenal tumors. In patients with biochemical confirmation of NCCAH genetic analysis of *CYP21A2* gene was performed.
Material and methods
One hundred patients, 22 males aged 62.8 (±9.9 years) and 78 females aged 61.9 (±8.4 years) with bilateral adrenal incidentalomas, treated in Department of Endocrinology, University Hospital in Cracow, were involved in the study. The median diameter of an adrenal tumor was 27.8 mm (±10.35 mm). All the tumors were accessed in CT scans as benign ones. In all patients basal and ACTH-stimulated 17-hydroxyprogesterone (17-OHP) serum concentrations were measured. The biochemical diagnosis of NCCAH was established in patients with the basal and/or stimulated 17-OHP level ≥10 ng/ml.
Results
Twenty-seven patients (27%) – five males and 22 females were diagnosed with NCCAH. Genetic screening was performed in 66.7% of all, in three cases changes in *CYP21A2* gene were revealed.
Conclusions
1. NCCAH should be taken into consideration in patients with bilateral adrenal incidentalomas.
2. Hormonal test results still play a crucial role in the diagnosis of NCCAH.
3. Genetic analysis of *CYP21A2* mutations maybe also useful in NCCAH diagnosis.

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P44

Adrenal insufficiency in treated PMR: The tip of the iceberg

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Background
Prolonged, high dose glucocorticoid therapy is used in to treat a number of rheumatological diseases, including polymyalgia rheumatica (PMR), giant-cell arteritis (GCA) and large vessel vasculitis (LVV). However there can be significant consequences of long-term glucocorticoid use, including iatrogenic adrenal insufficiency, due to suppression of the hypothalamic-pituitary-adrenal axis. This study aims to evaluate the prevalence, investigation and recovery of iatrogenic adrenal insufficiency in patients with PMR, GCA and LVV at a large UK teaching hospital.
Methods
We retrospectively identified patients seen in rheumatology outpatient clinics with a diagnosis of PMR, GCA or LVV, who had cortisol levels or short synacthen tests (SST) performed, between January 2014 and November 2017. Data were collected using a standardised proforma which included demographics, co-morbidities, maximal glucocorticoid dose and duration, clinical symptoms and details of investigations for adrenal insufficiency (i.e. SST results or cortisol values).
Results
We evaluated a total of 95 patients. The mean duration of prednisolone use was 4 years, 3 months (range 11–204 months). Over 30% of patients used a peak dose of prednisolone greater than or equal to 40 mg. 72% of all patients had symptoms possibly consistent with adrenal insufficiency. In total, eighty patients had a SST, mostly via the rheumatology department. On retrospective review of the SST results by a consultant endocrinologist, 33% of all tests were found to have sub-optimal cortisol levels. However 17.5% of baseline SSTs were not conducted appropriately. Of the patients who were found to have abnormal results, only 35% went on to have a repeat SST. 54% of the repeat SSTs showed normal adrenal function. Of the asymptomatic patients, 51.9% ($n=14$) had baseline tests consistent with adrenal insufficiency. The mean time to adrenal recovery overall, from baseline test was 18 months. 18% of patients with evidence of adrenal insufficiency had their prednisolone switched to a shorter acting glucocorticoid. Despite having an abnormal SST result, 43% patients were not referred to an endocrinologist.
Conclusion
Our study suggests there is a high prevalence of adrenal insufficiency in both symptomatic and asymptomatic groups in this patient population. The vast majority of patients with abnormal SST results did not have suitable follow-up tests and a large proportion were not referred to endocrinology. These results suggest the need for a joint pathway of care for evaluation of adrenal insufficiency in this patient group. Further studies, evaluating the optimal intervention strategies to aid adrenal recovery are also needed.

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P45

Decreased quality of life in male patients with primary adrenal insufficiency of Indian origin

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Background
In contrast to patients of European origin, primary adrenal insufficiency (PAI) in Indians is more common in males and often results from infectious etiologies (tuberculosis, Histoplasmosis). Most patients are treated with prednisolone, rather than hydrocortisone (HCT). A poor quality of life (QOL) has been reported in European patients with AD, but not in other populations. A few studies have also reported a high frequency of hypogonadism in PAI.
Objectives
To study the QOL and frequency of hypogonadism in Indian male patients with PAI.
Methods
In a cross sectional study, we recruited 37 male patients with PAI (age median (range) 53 (26–64) years; duration of illness 5.8 (1.4–28) years; 95% on prednisolone; 57% with infectious etiology). All patients were administered the short form SF36v2 questionnaire, previously validated in Hindi, to assess their QOL. A questionnaire regarding more specific symptoms of hypogonadism was also administered. An early morning serum total testosterone (T) was collected; in patients with low T (<10.4 nmol/l), the test was was repeated. Age, sex and, body mass index matched healthy controls ($n=76$) were studied.
Results
When compared with controls, patients had a highly significant reduction in QOL in each individual domain of SF36v2 ($P<0.001$), and in the summary physical ($P<0.001$) and mental component ($P<0.04$) domains. Twenty five (65%) patients had at least 1 symptom, while 17 (46%) had ≥3 symptoms suggestive of hypogonadism. However, only 5 (13.5%) patients had T<10.4 nmol/l. On multivariate analysis, the average daily glucocorticoid dose (hydrocortisone equivalent/m^2) was strongly associated with decreased QOL across most domains, while T2DM and increasing age were associated with poor QOL in a few domains. However, serum testosterone did not predict QOL.
Conclusion
A poor QOL was noted in all domains in male patients with primary adrenal insufficiency. A higher daily glucocorticoid dose was independently associated with poor QOL in most domains. While symptoms of hypogonadism were frequent, the frequency of decreased serum testosterone was low.

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P46

The measurement of the renin–angiotensin–aldosterone system in patients with adrenal tumors with arterial hypertension

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Introduction
This problem has a major social and medical significance. The prevalence of secondary endocrine hypertension is around 40%, of which primary aldosteronism is up to 15% and is usually developed at working age. Despite of improvement of diagnostical two-step method of finding primary aldosteronism, none of these test results can be considered reliable because of false positive and false negative results. That's why the problem of endocrine hypertension diagnosis especially primary aldosteronism is still very important. We made a research of the renin–angiotensin–aldosterone system (RAAS) and urinary aldosterone excretion in patients with arterial hypertension and adrenal tumors to improve diagnosis of primary aldosteronism.
Objective
To explore the renin–angiotensin–aldosterone system (RAAS) and 24-h urinary aldosterone excretion in patients with adrenal tumors and arterial hypertension.
Methods
We enrolled 59 patients with adrenal tumors in combination with arterial hypertension [blood pressure ≥ 140/90 mm Hg by antihypertensive drug classes, 85% females, age 52±12.5 years (mean±standard deviation)], who had hormone-producing adenomas (aldosterone-producing adenoma $n=27$, cortisol-producing adrenal adenoma $n=8$ and pheochromocytoma $n=5$) and non-functioning adrenal adenomas in combination with arterial hypertension ($n=19$). The RAAS (angiotensin II, angiotensinogen, prorenin) of plasma and serum is measured in peripheral blood by Enzyme Immunoassay**,** and aldosterone is determined in 24-hour urine by Enzyme Immunoassay.

Results
Patients with aldosterone-producing adenoma ($n=27$) in compared with non-functioning adrenal adenomas in combination with arterial hypertension ($n=19$) didn't have different results of RAAS: angiotensin II ($P=1.0$, median 29.6 pg/ml, interquartile range 23.4–35.6), angiotensinogen ($P=1.0$, median 15.4 µg/ml, interquartile range 13.5–18.8) and prorenin ($P=0.351$, median 688.5 pg/ml, interquartile range 418–1133.5). Though 24-h urinary aldosterone level in patients with aldosterone-producing adenoma ($n=27$) were statistically significantly higher than in patients with non-functioning adrenal adenomas with arterial hypertension ($n=19$) ($P=0.042$, median 17.1 µg/day, interquartile range 9.6–31.1).
Conclusion
24-h urinary aldosterone level may be diagnostically helpful in discriminating to clarify the diagnosis of primary aldosteronism, which, along with the definition of aldosterone-renin ratio (ARR) and confirmatory tests, can be a diagnostic criterion for diagnosing.

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P47

The renin-angiotensin-aldosteron system in primary adrenal insufficiency

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Background
Despite adequate hormone replacement therapy, evidence suggests that mortality is increased in patients suffering from primary adrenal insufficiency (AI), mainly because of cardiovascular diseases. Since activation of the renin-angiotensin-aldosteron system (RAAS) plays an important role in the development of hypertension and cardiovascular disease we aimed to investigate, if there are differences in AI compared to healthy controls.
Methods
Eight patients with AI (female $n=5$; male $n=3$; age 56 ± 21; BMI $22{,}8\pm2{,}8$ kg/m^2; mean blood pressure 140/83 mmHg)) and eight matched healthy volunteers (female $n=5$; male $n=3$; age 52 ± 21; BMI $25{,}2\pm4{,}3$ kg/m^2; mean blood pressure 135/84 mmHg) were included. Blood was drawn in the morning in the fasting state to measure serum electrolytes, renin-, aldosterone, cortisol and ACTH concentrations. Assessment of physiologically active angiotensin concentrations and equilibrium analysis was performed by RAS fingerprint measurements.
Results
In patients suffering from AI RAAS activity was increased with significantly elevated concentrations of renin ($P=0.027$), angiotensin-1 ($P=0.022$), angiotensin-2 ($P=0.032$), angiotensin-1-7 ($P=0.03$) and angiotensin-1-5 ($P=0.03$), as well as in a reduction in aldosteron-angiotensin-2 ratio (AA2-Ratio, $P=0.003$) compared to controls, resulting in a characteristic RAAS fingerprint. Plasma renin activity was strongly correlated with the sum of angiotensin-1+ angiotensin-2 ($r=0.983$; $P<0.01$).
Conclusions
AI is associated with a unique RAAS fingerprint. Physiologically active angiotensin concentrations are highly elevated, despite adequate hormone replacement therapy. This might contribute to the reported increased cardiovascular risk and should be investigated in future trials.

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P48

Percutaneous microwave ablation of adrenal remnant tissue. A novel treatment modality for persistent Cushing's disease

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A 29-year-old lady presented with features of Cushing's syndrome in October 2014. Investigations confirmed ACTH–dependent Cushing's syndrome. An MRI scan showed a 4.5 mm right-sided pituitary lesion and subsequent inferior petrosal sinus sampling confirmed a central source of ACTH hypersecretion. She underwent trans-sphenoidal pituitary surgery in January 2015. Histology confirmed a corticotroph adenoma with a Ki-67 proliferation index of 1%. However, a mean cortisol of 298 nmol/l on a cortisol day curve was highly suggestive of persistent hypercortisolaemia. MRI scanning confirmed small-volume residual tumour in the right anterior sella. She remained symptomatic and underwent a second trans-sphenoidal pituitary surgery in April 2015. Histology from this surgery showed normal adenohypophysis only. The second surgery was complicated with a post-operative CSF leak and meningitis. A cortisol day curve 6 weeks later showed a mean cortisol level of 474 nmol/l and further biochemistry investigations confirmed persistent hypercortisolaemia. Following MDT discussions, the patient underwent bilateral adrenalectomy in March 2016, with some difficulty encountered during removal of the left adrenal gland. As expected, histology of both adrenals showed evidence of adrenal hyperplasia. She was commenced on Prednisolone and Fludrocortisone postoperatively. She continued to have difficulty losing weight 5 months post-adrenalectomy (went up to 119 kg). An overnight dexamethasone suppression test confirmed persistent Cushing's disease (9 am cortisol 383 nmol/l). Prednisolone was discontinued and she was commenced on Metyrapone. MRI Pituitary showed a right-sided pituitary adenoma extending between the intra- and supracavernous internal carotid artery segments. A Ga68 DOTATATE whole body PET CT showed appearance consistent with residual hyperplastic adrenal tissue in the left suprarenal region. She was discussed in the Pituitary and Adrenal MDT meetings where percutaneous ablative approach of the residual adrenal tissue was considered due to the risks associated with further pituitary surgery or pituitary radiotherapy, or repeat abdominal surgery. She underwent CT-guided microwave ablation of the left adrenal remnant (120W) in July 2017, following which she was re-started on Prednisolone. Following the procedure, she improved significantly both clinically and biochemically. Her weight went down to 109 Kg after 6 months. Morning cortisol went down from 476 to 168 nmole/l. This was accompanied by ACTH rise from baseline 492 to 1558 ng/l. This case illustrates that percutaneous ablative approach of adrenal remnant tissue and possibly entire adrenal glands should be considered in the treatment of challenging Cushing's disease.

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P49

Risk estimator for autonomous cortisol secretion in adrenal incidentalomas. Retrospective study of 100 cases

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Purpose
A combined model of clinical, biochemical and radiological variables could help to predict autonomous cortisol secretion (ACS) in adrenal incidentalomas (AI).
Methods
We analyzed retrospectively 100 patients diagnosed of AI between 2011 and 2015. AI was defined as an adrenal mass >1 cm, accidentally discovered by radiologic examination. ACS was ruled out (ACS-) by serum cortisol post-dexamethasone suppression test (Nugent) <3 µg/dl, and was confirmed by levels ≥ 3 µg/dl, normal cortisoluria and no typical data of Cushing's syndrome. The statistical analysis was performed with STATA 13.0. For multivariate analysis variables were selected by a pvalue <0.1 on univariate analysis and previous literature findings.
Results
Ninety-three patients were included in the statistical analysis. Mean age was 62.9 years and 54% were women. Fourteen patients (15%) had ACS. In the univariate analysis, the variables associated with higher risk of ACS (expressed in odds ratio (OR) and/or the proportion/mean of the variable in ACS and ACS-) were: Nugent test (3.6 vs 1.5 µg/dl, $P<0.00$) and maximum adenoma diameter (MAD) (26.8 vs 17.2 mm, $P=0.02$). Higher risk of ACS was not related with age (64 vs 63 years, $P=0.57$), sex (ratio of masculinity 1.4 vs 0.8, $P=0.4$), HTA (OR 1.7, 71.4 vs 44.9%, $P=0.08$), diabetes (OR = 1.4, 36 vs 25.6%, $P=0.4$), obesity (OR = 0.6, 25 vs 37.6%, $P=0.4$), osteoporosis (OR = 1.3, 9.1 vs 7.2%, $P=0.8$), glucose (108.3 vs 105.5 mg/dl, $P=0.7$), cortisoluria (70 vs 59.7 µg/24 h, $P=0.5$), DHEAS (70.2 vs 46.2 µg/dl, $P=0.1$); ACTH (20.1 vs 18.2 pg/ml, $P=0.7$) or bilaterality (OR = 1.4, 20 vs 15%, $P=0.7$). No differences were found between ACS and radiological characteristics in the CT scan (calcification, necrosis, lipid content). In the logistic regression analysis, the variables male sex, age, HTA, diabetes, Nugent, DHEAS, MAD and bilaterality were included to elaborate the ACS predictor score. It was found that the model with the best predictive power for the ACS diagnosis included age, Nugent test and DHEAS levels, with sensitivity of 89% and specificity of 100%.

Conclusions
15% of AI in our series had ACS. We identified Nugent test and MAD as predictors of ACS. The combined model with the best ACS diagnostic accuracy combined age, Nugent test and DHEAS levels, with a specificity of 100%. This combined score could be a very useful tool to identify ACS with a higher diagnostic value than the Nugent test alone regardless of the cutoff point used. Its high specificity makes it especially indicated in the screening of AI.

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P50

Is the adrenal vein sampling the gold standard diagnostic test for the subtyping of primary aldosteronism?

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Introduction
Primary aldosteronism (PA) is the most common cause of secondary hypertension (5–10%) and it is underdiagnosed. Less than 50% of patients with PA have hypokalemia. The tests for determinate subtype of PA are cross-sectional imaging (adrenal CT or MRI) and adrenal vein sampling (AVS). The AVS seems to be important to direct appropriate therapy and surgery is the preferred treatment for patients with unilateral disease.
Material and methods
We reviewed 29 patients with PA confirmed by saline infusión test (SIT) who underwent AVS. We described the baseline characteristics and the results of the AVS. We analyzed the concordance between imaging and AVS.
Results
Our study included 24 men (82.8%) and five women (17.2%) with a median age of 59.5 years (39–76). The median age of diagnosis of hypertension was 43 years (25–57) and the time passed until the diagnosis of PA was 13 years (1–26). The median body max index was 30.81 (21.44–47.80). Twenty-three patients had family history of hypertension (79.3%). The median value of blood pressure was: systolic 150 mmHg (130–192) and diastolic 90 mmHg (74–111). Twenty-three patients were treated with 3 or more antihypertensive drugs (79.3%). Twenty-six patients had hypokalemia (89.7%), with a median potassium of 2.9 mEq/L (2.4–3.9) and a median MDRD of 88.3 (47.1–106.2). 40% of patients had hypertensive retinopathy (8 of 20 patients examined) and 70.4% had left ventricular hypertrophy (19 of 27 patients examined). Cross-sectional imaging was normal in 10 patients (34.5%) and abnormal in 19 (65.5%): unilateral mass in 16 and bilateral masses in 3. AVS was lateralizing in 19 patients (65.5%), non-lateralizing in 5 (17.2%), indeterminate in 2 (6.9%) and technical AVS failure in 3 (10.3%). Imaging and AVS were concordant in 61.5% of patients. All patients who underwent surgery (adrenalectomy) normalized potassium (n = 15). After follow up, 20% of patients were completely cured (normotensive without antihypertensive drugs) and 80% demonstrated improvement (better blood pressure control or decrease in number of antihypertensive drugs).
Conclusions
The high percentage of hypokalemia suggests that PA is underdiagnosed in our area. The clinical suspicion is important because these patients have a much higher cardiovascular risk profile than patients with essential hypertension, and it is demonstrated by the high prevalence of left ventricular hypertrophy. Due to the poor performance of cross-sectional imaging, it is indicated to perform AVS as a better test for determination of PA subtype and decide the appropriate treatment.

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P51

A descriptive study of patients with adrenocortical carcinoma treated in hospital clinico san carlos (HCSC) over the last 20 years

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Introduction
Adrenocortical carcinoma (ACC) is a rare and aggressive tumor that accounts for 0.2% of cancer-related deaths. Case series and prospective studies are very limited due to its low prevalence. Current knowledge is based primarily on the opinions of experts in specialized units. The aim of this study is to perform a descriptive analysis of the management and prognosis of patients with ACC in HCSC in the last 20 years.
Material and methods
Eighteen cases of ACC between 1997 and 2017 in HCSC were retrospectively reviewed. All data were analyzed including demographic, epidemiological and clinical information using SPSS 15.0. The study obtained the approval of the local Ethics Committee.
Results
11/18 (61%) were male and the mean age was 54.8 (s.d. 15.3). Diagnosis was incidental in 5/18 (27.8%). The most common presentation (6/18, 34.6%) was constitutional symptoms. 39% of the tumors (7/18) were functioning; 2 patients presented Cushing's syndrome, 2 hyperandrogenism, 2 presented with both and 1 with hyperaldosteronism. In 2/18 (11%) serum hormone levels were not performed. 4/18 (22%) were never evaluated by an endocrinologist. All patients had CT performed, 5/18 (28%) had MRI, 4/18 (22%) had PET and MIBG-scintigraphy, and 7/18 (39%) had FNA. The mean size was 118.4 (s.d. 69.9) mm. 13/18 (72%) were located on the left side. Upon diagnosis, 9/18 (50%) and 5/7 (71.4%) of the functioning were in stage IV. 16/18 (89%) had surgery (open in 14/18, 87%). 12/18 (67%) received mitotane (between 1 and 57 months), whose plasma levels were monitored only in half of them. It was discontinued in 3/12 (25%) due to adverse effects. 7/18 (39%) received different lines of chemotherapy, 7/18 (39%) targeted therapies, 3/18 (16.6%) radiotherapy and 1/18 (5.5%) chemoembolization. 5/18 (28%) received only palliative care. 14/18 (78%) are deceased. Median survival time was 41 months (min 2 – max 92) with no significant differences according to stage (except stage I), functionality or use of mitotane therapy.
Conclusions
In our centre, ACC was an uncommon tumor with poor prognosis regardless of sex, stage (except in stage I), treatment applied or tumor functionality. It was usually diagnosed in middle-aged patients and in advanced stages. The most common treatments used were surgery and mitotane. We also noticed that there is a considerable lack of standardization in the treatment strategy of this tumor for advanced cases in our centre. Patients with ACC should be treated in highly specialized units by a multidisciplinary team.

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P52

Bilateral adrenalectomy for occult ectopic Cushing's syndrome in two patients with catastrophic hypercortisolism

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Introduction
Ectopic adrenocorticotropic hormone (ACTH) secretion is a less common cause of Cushing syndrome(CS) and is seen in 5 to 10% of patients with endogenous hypercortisolism. The most common types are bronchial carcinoids and small cell lung carcinoma. However, in approximately 10–20% of the cases, overt tumor cannot be found. Here, we described two patients with catastrophic hypercorticolism associated with ectopic CS and who were treated with bilateral adrenalectomy.
Case 1
A 47-year-old female patient had a history of a total abdominal hysterectomy and bilateral salpingo-oopherectomy operation due to clear cell ovary carcinoma 7 months ago. She was treated with chemotherapy. After 3rd dose chemotherapy, she had been hospitalized and treated due to sepsis associated with urinary tract infection. During the follow-up period in oncology, hypokalemia was detected and she was referred to our department due to severe muscle weakness in lower extremities and hypokalemia (serum K: 2.2 mEq/l). 24-h urinary free cortisol, ACTH measurement, dexamethasone suppression test (DST) demonstrated an ACTH dependent hypercortisolism. The inferior petrosal sinus sampling was indicative for an ectopic ACTH secretion. CT-scans of the thorax and abdomen, FDG-PET/CT scan and Ga68 DOTATATE PET/CT scans, were unable to demonstrate malignancy. Previous ovarian pathology was screened for ACTH secretion and evaluated as negative. Antifungal and metyrapone were started and then bilateral adrenalectomy was performed.

Case 2
A 71-year-old male patient who had a medical history of metastatic prostate carcinoma was referred to our department due to severe hypopotasemia, muscle weakness, refractory hypertension, peripheral edema. He had a history of second operation 3 months ago due to tumoral enlargement at the base of the urinary bladder and it was evaluated as infiltration of the prostate carcinoma. 24-h urinary free cortisol, ACTH measurement, DST demonstrated an ACTH dependent hypercortisolism. CT-scans of the thorax and abdomen, FDG-PET/CT scan and Ga68 DOTATATE PET/CT scans, were negative for malignancy. Medical therapy was started. But refractory hypertension, parenteral potasium infusion need were not suspended. Bilateral adrenalectomy was perfomed. He died due to pulmonary embolism 2 months after adrenalectomy.
Conclusion
Common treatmant options of Cushing syndrome consist of tumor management, somatostatin analogs, steroidogenesis inhibitors. Bilateral adrenalectomy is a highly effective treatment for patients with severe hypercortisolism if rapid control of hypercortisolism is desired. Mortality is high especially in patients with severe co-morbidities and mostly it depends on the prognosis of the underlying malignant tumor.

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P53

In vitro effects of KCNJ5 mutations on cellular death mechanisms

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Introduction
Primary aldosteronism (PA) is the most frequent form of endocrine hypertension and is commonly caused by an aldosterone producing adenoma (APA). Germline and somatic mutations in the *KCNJ5* gene have been found in up to 40% of APAs and demonstrated to play a crucial role in the pathophysiology of PA.
Aim
Here we characterize and investigate the effects of the most common *KCNJ5* mutations on cellular death mechanisms based on an *in vitro* model.
Methods
Cell lines in COS7 or HAC15 cells stably expressing KCNJ5 mutants (G151R, L168R, G151E, T158A) and a control cell line transfected with empty vector were established using a cumate-inducible PiggyBac vector system. Cell viability and cell death (necrosis and apoptosis) were determined by WST-1 assays or flow cytometry following induction with cumate.
Results
In COS7 cells, the KCNJ5 -G151E and -L161R mutants caused the highest proportion of cell death followed by -G151R and -T158A following cumate induction (0 μg/ml to100 μg/ml). Expression of KCNJ5-T158A in COS7 or HAC15 cells resulted in a similar loss of cell viability. All KCNJ5 mutants tested showed an increase in cell death by apoptosis or necrosis with necrosis causing a greater proportion of cell death than apoptosis, when induced with cumate (5 μg/ml and 25 μg/ml). The KCNJ5 mutations that induced the highest level of necrosis were G151E and L168R followed by G151R and T158A.
Conclusion
KCNJ5 mutations cause cell death mostly through necrosis, albeit to a different extent.

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P54

The role of DHEAS in the diagnosis of possible autonomous cortisol secretion by incidentally discovered adrenal adenomas

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Introduction
Although possible autonomous cortisol secretion (pACS) is the commonest endocrine dysfunction detected in patients with adrenal incidentalomas, the diagnosis of this condition is still challenging. Dehydroepiandrosterone sulfate (DHEAS) is an adrenal androgen secreted by adrenal glands under the regulation of ACTH. DHEAS does not follow a circadian rhythm and has a long half-life in serum. Because of these features, low blood concentration of DHEAS has been recently investigated as a screening marker of pACS. Nevertheless, data regarding the diagnostic accuracy of DHEAS to predict pACS are sparse and contradictory.
Methods
74 patients with adrenal incidentalomas were evaluated in the context of ERGO trial (NCT02611258). Clinical, hormonal and radiological assessment were performed to exclude Cushing's syndrome, pheochromocytoma, Conn syndrome, adrenocortical carcinoma, late-onset congenital adrenal hyperplasia, myelolipoma and metastasis. Cortisol levels after a 1-mg overnight dexamethasone suppression test between 51 and 138 nmol/l, confirmed by 48-h Liddle tests, were used to classify patients as pACS. DHEAS ratios were calculated by dividing the DHEAS by the lower limit of the respective reference range according to age and gender.
Results
36 patients were diagnosed with adrenal adenoma associated with pACS (pACS group) and 38 with non-functioning adrenal adenoma (NF control group). There were no difference in age (pACS: 65.8 ± 11.3 years; NF: 64.03 ± 11.0 years; $P = 0.560$), body mass index (pACS: 27.71 ± 5.5 kg/m^2; NF: 27.8 ± 4.2 kg/m^2; $P = 0.942$), and sex (pACS: female 23/31; NF: female 17/33; $P = 0.110$) between the two groups. Mean DHEAS ratio was significantly lower in the pACS compared to the NF group (pACS: 1.24 ± 1.55; NF: 2.68 ± 0.86; $P < 0.001$). Furthermore, there was a negative correlation between the post-dexamethasone cortisol levels and DHEAS ratio ($r = -0.382$; $P = 0.002$). ROC analyses [AUC 0.837 (0.737–0.936); $P < 0.0001$], showed that a DHEAS ratio of 1.56 suggested a sensitivity of 81% and specificity of 71% for the diagnosis of pACS with a positive predictive value of 73.5%, a negative predictive value of 78.6% and reaching an accuracy of 75.8% in predicting pACS.
Conclusion
Our study shows that DHEAS ratio may contribute to the diagnostic work-up in patients with adrenal incidentalomas. A single basal measurement of age and gender-adjusted DHEAS ratio could be included as an advantageous screening test for the detection of possible autonomous cortisol secretion. Further studies are needed to confirm the role of DHEAS screening in the diagnostic evaluation of pACS.

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P55

Abnormal salivary cortisol result in patient with low probability of Cushing disease

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We presenting a case of 26 old lady who is known to have Denys-Drash syndrome, epilepsy and bronchial asthma who presented with history of recent significant weight gain, extensive abdominal bruising and significant muscle weakness which she described literally as not able to use her upper limbs to move to help shuffle her bottom in the floor, a manoeuvre that she was able to do before. Patient is on Carbamazepine, sodium valporate, levetiracetam , salbutamol and Pulmicort inhalers (budesonide), Laxido,And Midazolam. On examination patient was normotensive, a degree of the abdominal striate, proximal muscle weakness could not be elicited clinically. The general practitioner enquired whither the patient presentation could be a manifestation of Cushing syndrome,in this pateint the modality of investigation need to be selected carefully, patient is already on Carbamazepine which could affect both UFC and plasma cortisol as it is interferes of the chromatographic methods and can also induce hepatic clearenece of Dexamethasone, so salivary cortisol was chosen for this test, but the result showed significant high cortisol level in many different occasions (see table below), after further questioning it appears that the patient was using the Pulmicort inhaler before having the test,this lead to the significant high cortisol found.
Discussion
Salivary cortisol measurement is well established method to measure plasma free cortisol concentration, aiding the diagnosis of cortisol excess and deficiency state,it had the advantage of being free from the interference of physiological or pathological effect of CBG /albumin, ease of sampling, and lack of the stress of venepuncture. The required standered is to obtain the salivary sample using collection of passive drooling saliva or asking patient to chew a cotton pledget – (Salivette®). Salivary samples should not be collected within 30 min of brushing teeth, drinking. No ingestion of any foods of animal origin within 3 h prior collection. Any sample with blood contamination should be discarded, smoking affect salivary 11beta-hydroxysteroid dehydrogenase type 2, this increases

salivary cortisol so it should be avoided on the day of the test. The potential steroid contamination of the sample including topical or inhaled steroid is something we need to be careful with when interpreting the salivary cortisol result this was clearly missed in this case.

14/07/17	2.4	2.4 nmol/l
16/07/17	23:00	>80 nmol/l
24/08/17	23:00	31.6 nmol/l

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P56

Improved salivary cortisol rhythm with dual-release hydrocortisone

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Introduction and aim
The purpose of replacement therapy in Adrenal Insufficiency (AI) is mimicking endogenous cortisol levels as closely as possible: dual release hydrocortisone (DR-HC) has been introduced to replicate the circadian cortisol rhythm. Multiple daily saliva collections could be used to assess the cortisol concentration during real-life: our aim was to study the salivary cortisol rhythm in AI.
Materials and methods
We prospectively evaluated, in an observational study, 18 outpatients with AI (11 primary and 7 secondary AI), switched from conventional treatment (conv-HC, 25 mg/day) to the same dose of DR-HC. We collected 6 samples of saliva in a day, measuring cortisol (F) and cortisone (E) with LC-MS/MS. 43 matched healthy subjects served as controls. To assess endogenous daily F exposure we computed the Area Under the Curve (AUC) for salivary F levels at the different time-points respect to the ground (SalAUC) according to the trapezoidal formula. We divided the day in two different parts, the first covering the morning ($SalAUC^{morning}$), and the second covering the afternoon and the evening ($SalAUC^{afternoon}$).
Results
F levels of patients during conv-HC and after switch to DR-HC were similar in the morning, and lower in the afternoon/evening with DR-HC. Considering daily cortisol exposure, SalAUC was lower with DR-HC despite assuming the same GC dose. Specifically, morning $SalAUC^{morning}$ levels were similar among conv-HC and DR-HC, contrariwise $SalAUC^{afternoon}$ was lower with DR-HC. Morning F was lower in patients than controls: a value <3 nmol/l presented 90% SE and 98% SP in detecting patients (AUC 0.979). Also morning E levels were able to differentiate AI from controls: E <9.45 nmol/l presented 95% SE and 94% SP to detect patients with AI (AUC 0.982). Cortisol rhythm in patients with DR-HC was closer to controls, especially in the afternoon/evening: normalization of evening cortisol exposure ($SalAUC^{afternoon}$) was observed only in patients with DR-HC. F to E ratio levels were similar between patients with conv-HC and DR-HC, and allowed us to exclude glucocorticoid contamination. A reduction of total cholesterol levels was observed with DR-HC; HbA1c levels dropped with DR-HC in diabetic patients (57 to 52 mmol/mol, $P=0.045$).
Conclusions
Salivary cortisol is a reliable tool to assess the improvement of cortisol profile in patients treated with DR-HC, and might provide new insights in the study of patients with AI.

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P57

A case of adrenal Cushing's syndrome initially presenting with diabetic ketoacidosis

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A 49-year-old female was admitted to medical HDU with diabetes ketoacidosis (DKA) and newly diagnosed diabetes. Six months previously she was diagnosed with malignant hypertension. She had poorly controlled blood pressure despite treatment with four anti-hypertensives, which were her only regular medication. She had never used any medications or creams containing glucocorticoids. She had no history of hypokalaemia and reported no use of liquorice. She recently attended an outpatient appointment with a cardiologist and investigations including MRA of renal arteries and echocardiogram were all reported as normal. She complained of a 6-month history of lethargy, severe weight gain, and a two-month history of easy bruising, lower-limb weakness, and increasing polyuria and polydipsia. There was no history of headache, palpitations, flushing, or diaphoresis. On examination, she had a BMI of 41 kg/m^2, she had multiple bruises, off-color abdominal striaes, and proximal myopathy evident on lower limbs. She had no signs of androgen excess. Upon transfer to a general medical ward she was under the care of the endocrinology team. IFCC-HbA1C checked on admission was 102 mmol/mol, showing a large increment when compared to 30 mmol/mol measured 6 months previously. Anti-glutamic acid decarboxylase and anti-islet cell antibodies were both negative. Cortisol level post overnight-dexamethasone suppression was high at 163 nmol/l (RR <50 nmol/l). Total urine cortisol was 472 nmol in 24hours, confirming hypercortisolaemia. Tests were done when renal function was normal. Adrenal CT revealed a 2.6 cm right-adrenal adenoma (absolute washout=69%). 24-h urine metanephrines (×2) and aldosterone-renin-ratio were all within normal range. ACTH level was 15.9 ng/l (RR: 0–46). Adrenal androgen measurements are still being processed. In view of her inconclusive ACTH results, an MRI of the pituitary has also been requested and it is still pending. She was discharged on basal-bolus insulin and regular anti-hypertensives with a plan for urgent follow up in endocrinology clinic and discussion of results on adrenal MDT. This is a case of rapidly developing Cushing's syndrome leading to life-threatening presentation with malignant hypertension and DKA. Glucose intolerance associated with Cushing's syndrome is usually only mild to moderate in severity. Marked hyperglycaemia, glycosuria, and polyuria are uncommon, and ketosis is rare. Appropriate management could potentially lead to total remission of diabetes and hypertension.

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P58

The diagnostic accuracy of increased late night salivary cortisol for Cushing's Syndrome: a real-life prospective study

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Introduction and aim
A prompt diagnosis of Cushing's Syndrome (CS) in high-risk populations is mandatory: 1-mg dexamethasone suppression test (1-mg DST); late night salivary cortisol (LNSC) and urinary free cortisol (UFC) are recommend, despite thresholds calculated in retrospective studies. Our aim was to study the diagnostic accuracy of LNSC measured with chemiluminescence assay in a prospective study, confirming discrepancies with mass spectrometry (MS).
Materials and methods
We enrolled 117 controls and 164 suspected-CS (final CS=47, non-CS=117). In case of increased LNSC, high clinical suspicion of CS or adrenal incidentaloma, patients were hospitalized in order to exclude/confirm CS.
Results
We found a large number of false positive results: 35 out of 81 subjects with increased LNSC were non-CS (15 diabetic and 20 obese patients). 2 out of 29 patients with adrenal incidentaloma presented an impaired serum cortisol rhythm. Considering 16 nmol/L as threshold for CS diagnosis, overall LNSC revealed sensitivity (SE) of 97% (95% CI 0.817–0.993) and specificity (SP) of 84% (95% CI 0.772–0.871) in the whole group of subjects considered. If we considered the group of non-CS (those patients with increased likelihood to have a CS), the number of false positive results increased, and therefore the SP decreased to 70% (95% CI 59.8–76.3). SP dropped to 60% (95% CI 49–68.3) if we discharged patients with adrenal incidentaloma. Therefore, we re-computed the threshold of LNSC only in the group of CS compared to non-CS: increasing the cut-off (21.9 nmol/l) we gained in SP (77%) and lost in SE (92%). We measured cortisol with MS in those patients with increased LNSC results in chemiluminescence or high clinical suspicion of CS. MS confirmed the false negative LNSC result of the one patient with confirmed CS and normal cortisol rhythm with chemiluminescence (respectively 1 and 0.6 nmol/l). Considering the 35 non-CS subjects with false positive increased LNSC in chemiluminescence, in half cases MS analyses revealed a normal LNSC.
Conclusions
LNSC measured in automated chemiluminescence is reliable in clinical practice: it present a high diagnostic accuracy to exclude hypercortisolism in patients with normal cortisol levels. MS could be used to reduce the number of false positive

results, nevertheless some non-CS subjects with functional hypercortisolism could have a mild impairment of cortisol rhythm.

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P59

Cardiovascular features of possible autonomous cortisol secretion in patients with adrenal incidentalomas

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Introduction
Low-grade incomplete post-dexamethasone cortisol suppression in patients with adrenal incidentalomas, recently redefined as possible autonomous cortisol secretion (pACS), has been associated with increased cardiovascular events and mortality. However, prospective studies documenting cardiac abnormalities in these patients are lacking.
Methods
In the context of ERGO trial NIH (NCT02611258), between July 2016 and September 2017, 71 consecutive patients with adrenal lesions were prospectively screened for hypercortisolism by dexamethasone suppression test. Complete anthropometric, metabolic and hormonal parameters were recorded along with full cardiac ultrasound assessment and noninvasive measurement of arterial stiffness. All patients underwent chemical-shift magnetic resonance imaging to characterize the adrenal lesions. Cardiovascular outcomes were recorded in blind.
Results
According to post- dexamethasone suppression cortisol values (post-DST), 34 patients had pACS and 37 non-functioning adenomas (NFA). The two groups were similar in sex, BMI, age distribution, cardiovascular risk factors and comorbidities. Left ventricular mass index (LVMI) was increased in pACS compared to NFA ($P=0.006$), and correlated to the post-DST cortisol level ($r=0.347$; $P=0.004$). The post-DST cortisol levels explained up to 7.3% of LVMI variance ($P=0.018$). Compared to NFA, patients with pACS had a higher prevalence of diastolic dysfunction (35.1% vs 82.6%; $P=0.001$), and worse arterial stiffness assessed through pulse wave velocity ($P=0.033$).
Conclusions
In apparently asymptomatic patients, mild autonomous cortisol secretion can sustain early cardiac and vascular remodeling, independently of other risk factors. The morphological and functional cardiovascular changes observed in pACS underline the need for further studies to correctly define the long-term management of this relatively common condition.

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P60

Expert patients are better prepared to survive adrenal crisis than most – but still lack training in injection method

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We examined online questionnaire responses received Dec 2017 – Jan 2018 from a sample of well-informed adrenal patients belonging to the Addison's Disease Self-Help Group (N=374). ADSHG members reported levels of preparedness to self-manage during adrenal emergencies that were strikingly higher than any UK clinic survey.

- 88% reported wearing medical jewellery
- 80% had an in-date injection kit with them at the time of their most recent adrenal emergency
- 74% carried an ADSHG emergency steroid alert card

Familiarity with injection method was disappointingly low even in this "expert patient" cohort.

- 40% had viewed the ADSHG's online injection demonstration videos
- 36% had received 1- 1 injection training from an endocrine nurse
- 22% had received 1-1 injection training from a GP or practice nurse
- 15% had practiced injection method at an ADSHG group meeting

Educational materials launched by ADSHG since its previous member survey in 2013 appear to have made only a modest, positive contribution to patient competence in injection method (Table 1).

Table 1

Who gave injected hydrocortisone for most recent adrenal emergency	2013 N=300	2017 N=160	*P* value
Myself or family member	36%	46%	$P=0.022$
Pre-hospital or hospital clinician	59%	50%	$P=0.027$

These findings emphasize that endocrine units could do more to address patient safety. Ensuring all steroid-dependent patients are well-equipped and trained in how to survive adrenal crisis requires more systematic attention and resourcing across all clinics.

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Histopathological characteristics of lipid-poor adrenal adenomas

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Background
Up to 30% of incidentally-discovered adrenal masses are lipid-poor adenomas (LPA). The clinical significance of LPA is poorly understood. The aim of the study was to investigate histopathological features of LPA and their association with radiological parameters.
Methods
A total of 39 patients with radiological evidence of LPA were included. LPA was defined as an adrenal mass with pre-contrast Hounsfield units (HU) ≧10, associated with absolute washout >60% or relative washout >40% after contrast infusion. Patients underwent hormonal work-up for primary aldosteronism (aldosterone/plasma renin activity ratio >30 in orthostatic position and after Captopril test) and pheochromocytoma (elevated urinary metanephrines). Hypercortisolism was defined as cortisol levels after 1 mg-dexamethasone suppression test >50 nmol/l. F18-Fluoro-Deoxy-Glucose (FDG)-PET scan was performed in 31/39 patients. In resected tumors, Weiss, Lin-Weiss-Bisceglia, and PASS score were calculated, where appropriate.
Results
Radiological characteristics of the population were as follows (mean±SD): tumor diameter 23.0±10.9 mm, pre-contrast density 27.5±10.2HU, absolute and relative washout 68.1±7.6% and 50.7±7.5%, respectively, and FDG-PET scan 6.1±4.6 SUV. Hormonal evaluation showed Cushing's syndrome in 7/39 patients (18%), subclinical hypercortisolism in 11/39 subjects (28%), primary aldosteronism in 2/39 patients (5%) and elevated metanephrines in 2/39 subjects (5%). The remaining cases (17/39, 44%) were non-secreting. Eighteen patients underwent adrenalectomy because of tumor diameter ($n=2$), hormonal hypersecretion ($n=9$) and high FDG-PET SUV (n=7). Histopathological examination showed adrenocortical adenoma in 12/18 cases (66%) and adrenocortical carcinoma in 3/18 tumors (17%), as defined by Weiss score. Hemangioma was diagnosed in 1/18 cases. The two remaining tumors were pheochromocytoma (PASS score 3 and 7). Among all adrenocortical tumors, abundant granular eosinophilic cytoplasm was found in 11/15 cases (73%). By applying the Lin-Weiss-Bisceglia score, one tumor was confirmed malignant, whereas 3/11 tumors were borderline. Weiss score was positively associated with pre-contrast density (Odds Ratio [OR] 1.088, 95% Confidence Interval (CI) 1.018–1.163, $P=0.013$) and absolute washout (OR 1.105, 95%CI 1.005–1.216, $P=0.039$). Lin-Weiss-Bisceglia score was positively associated with tumor diameter (OR 1.045, 95%CI 1.015–1.076, $P=0.003$) and pre-contrast density (OR 1.046, 95%CI 1.002–1.091, $P=0.039$).
Conclusion
LPA represents a heterogeneous class of tumors, which may include pheochromocytoma and adrenocortical carcinoma. In our pilot study, 5/18 (28%) LPAs were classified as malignant or borderline at histopathological analysis. Eosinophilic cytoplasm is a common finding in those tumors and Lin-Weiss-Bisceglia score may be used to avoid overdiagnosis of malignancy.

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Different biological and functional features in patients with Cushing's disease harboring micro- or macro-adenomas

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Background
ACTH-secreting pituitary adenomas represent two-thirds of Cushing's syndrome (CS), the so-called Cushing's disease (CD). These tumors are sometimes > 10 mm in maximal diameter (macro-CD), but the majority of them are < 10 mm (micro-CD). The aim of this study was to compare baseline characteristics of patients with micro-CD and macro-CD.
Materials and methods
Clinical, hormonal and radiological data of 226 patients with CD were retrospectively collected (195 females, mean age 43 ± 13 years; micro-CD $n = 195$, macro-CD $n = 31$) in two Italian referral centers for CS. Surgical remission was defined in case of hypocortisolism (morning serum cortisol < 50 nmol/l) early after surgery and need for substitutive glucocorticoid treatment for at least 4 months. Data are presented as mean and standard error (m/SE), $P < 0.05$ was considered significant.
Results
Basal ACTH levels were higher in patients with macro-CD (160/44 vs 60/4 ng/l, $P < 0.001$), however basal cortisol levels were similar (645/20 vs 710/81 nmol/l), therefore ACTH-cortisol ratio was higher in macro-CD (0.21/0.03 vs 0.09/0.01, $P < 0.001$), suggesting that macro-corticotropinomas might secrete non-functional corticotrophin, considering the increased ACTH secretion in macro-CD. Regarding dynamic tests, ACTH peak after CRH was double in micro-CD (+195/18 vs +99/17%, $P < 0.05$), despite similar cortisol peak: we could speculate that only the normal corticotroph cells are able to generate a significant response to CRH. Response to desmopressin test and adrenal feedback to low (1 mg) or high doses (8 mg) of dexamethasone test were preserved (mean cortisol suppression 72% in both groups after 8 mg). Late night salivary cortisol, midnight serum cortisol and urinary free cortisol (normalized for upper limit of normality) were similar among two groups, as well as clinical collected data (blood pressure, glucose metabolism, lipid profile, sodium/potassium levels, gender and age). In a subset of patients ($n = 125$) at least 2 years of follow-up were available: the surgical remission rate was similar between subjects with micro- and macro-CD.
Discussion
Patients with micro- and macro CD presents, despite their clinical similarities, have different biological and functional features, thus not affecting the outcome of neurosurgery.

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Salivary cortisol as a diagnostic tool for hypercortisolism in Cushing's syndrome and adrenal incidentaloma

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Background
The lack of circadian rhythm is a marker of Cushing's syndrome (CS). Therefore, salivary cortisol rhythm has been suggested for studies on the hypothalamic–pituitary–adrenal (HPA) axis. Late-night salivary cortisol has been used recently by many centers as a first line diagnostic test for CS, yet its accuracy is still on debate.
Aim
To evaluated the performance of morning and late night salivary cortisol in patients with CS and adrenal incidentaloma (AI).
Patients and methods
We performed a case-control study including asymptomatic patients with AI in whom CS was rule out (with other screening and diagnosis tests) and patients with confirmed CS and analyzed morning (MSC) and late-night salivary cortisol (LNSC) levels and MSC-to-LNSC difference. We assessed the accuracy of LNSC in the CS screening, considering as a cut-off a 0.350 μg/dl, previously validated by our laboratory. Statistical analysis was performed using SPSS v22.0, considering statistical significance at the 0.05 level.
Results
We included 81 patients with AI and 11 patients with CS (ten patients with active Cushing's disease and one patient with ectopic CS). The majority of patients were female in both groups (61.7% and 81.8%, $P = 0.167$ in AI and CS, respectively), but patients with AI were older than CS patients (66 years, min-máx 38–92 vs 55 years, min-máx 28–75; $P < 0.05$). The LNSC median level was significantly higher in the group of patients with CS (0.634 μg/dl (min-máx 0.192–1.280) vs 0.230 μg/dl (min-máx 0.054–1.140); $P < 0.001$) but no significant differences were found in median MSC levels among the two groups (0.735 μg/dl (min-máx 0.266–2.210) vs 0.506 μg/dl (min-máx 0.054–2.590); $P = 0.084$). The median MSC-to-LNSC difference was 0.740 μg/dl (min-máx −0.46–0.93) in CS patients and 0.322 μg/dl (min-máx −0.78–2.46) in AI patients ($P = 0.051$). LNSC above 0.350 μg/dl achieved a sensibility of 90.9% and a specificity of 77.8% in the diagnosis of CS, with positive and negative predictive values of 35.7% and 98.4%.
Conclusions
In this population, patients with CS presented LNSC levels significantly higher than patients with AI, but MSC levels and the MSC-to-LNSC difference weren't significantly different between the two groups. The cut-off of 0.350 μg/dl to the LNSC presented a good accuracy with a very high NPV and it's a useful tool for the diagnosis of CS.

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Bilateral macronodular adrenal hyperplasia with autonomous cortisol secretion

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Introduction
Bilateral macronodular adrenal hyperplasia is a rare cause of Cushing's syndrome (CS) characterized by multiple adrenal nodules >1 cm. It can be diagnosed in patients with overt CS but is more often diagnosed incidentally, especially in the 5th or 6th decades of life.
Clinical case
61-year-old woman with type 2 diabetes, arterial hypertension and dyslipidemia treated with metformin + sitagliptin 1000/50 mg bid, valsartan + hydrochlorothiazide 160/25 mg qd, bisoprolol 2.5 mg qd, atorvastatin 20 mg qd. Irrelevant family history. After right hemicolectomy for a colon polyp with high-grade dysplasia she performed a CT scan which showed nodular thickening of the adrenal glands with bilateral hypodense nodules, the largest in the right adrenal gland with 32 mm and in the left with 31 mm. She was referred to the Endocrinology appointment. She complained of anxiety and fatigue. At physical examination: weight 66.8 kg, height 150 cm, BMI 29.7 kg/m^2, arterial pressure 159/93 mmHg, heart rate 77 bpm, central obesity, thin limbs; no reddish purple striae, facial plethora, easy bruising, dorsocervical fat pad or proximal myopathy. Biochemical study showed high serum cortisol levels after 1-mg overnight dexamethasone suppression test (DST) in two separate measurements (24.7 and 20.4 μg/dl), absence of cortisol suppression after the longer dose DST (serum cortisol 14.4 μg/dl), late-night serum cortisol of 11.4 μg/dl, normal urinary free cortisol in two separate measurements ((59.4; 34.5; 62.1 μg/day (N:4.3–176.0)) and morning serum ACTH of 1.0 ng/l in two measurements. Bone mineral density was normal. A follow-up CT scan showed enlargement of the adrenal glands, which contained multiple spontaneously hypodense and bilateral nodules, measuring the largest one 3 cm in the right side and 3.1 cm in the left. The nodules were well delimited, without interstitial calcifications, suggestive of multiple adrenal adenomas. The investigation for ectopic adrenal receptors was negative.
Discussion
This is a case of bilateral macronodular adrenal hyperplasia with autonomous cortisol secretion. The patient symptoms and comorbidities may be related to excessive cortisol secretion. In the absence of a clear picture of CS adrenalectomy is not recommended. However, unilateral adrenalectomy of the largest lesion is a possibility. In this case, since there was no overt CS, the comorbidities were controlled under medical treatment and there was similar involvement of both glands, we decided for active surveillance to avoid the consequences of bilateral adrenalectomy.

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P65

A systematic survey of low S-cortisol levels at the department of clinical chemistry: indications for testing and frequency of undiagnosed adrenal insufficiency

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A systematic survey of low S-cortisol levels at the department of clinical chemistry: indications for testing and frequency of undiagnosed adrenal insufficiency.

Background

S-cortisol is frequently analyzed at clinical chemistry departments. Low levels of S-cortisol needs to be promptly acted on if the cause is undiagnosed adrenal insufficiency (AI). The causes of S-cortisol testing are however multiple and low levels are necessarily not alarming if found in patients already under clinical evaluation or surveillance. Consequently, far from all clinical chemistry departments have as routine to alert clinicians on low S-Cortisol, potentially delaying AI diagnosis.

Aim

To identify individuals with S-cortisol $<$ 150 nmol/l and determine the indication for testing and the number of cases of undiagnosed AI.

Material and methods

We retrospectively went through the results from all S-Cortisol analyses performed at the Clinical chemistry department at the Karolinska university hospital during six months, January 1 until June 30 2013. Individuals with S-cortisol $<$150 nmol/l were identified and their medical records were reviewed to determine the indication for S-cortisol testing.

Results

993 S-cortisol analyses $<$150 nmol/l were identified. Medical records were available from 866 individuals (female 539, children 94). The most common indication for the S-cortisol testing was dexamethasone inhibition test n 334, followed by monitoring of pituitary insufficiency n 62. In 146 patients the indication for testing was unclear and not stated in the records. In 2% (*n* 19) of the patients previously undiagnosed AI was identified. Many patients were severely ill at the time of testing, 78 (9%) later deceased from other causes than AI, but in one case, undiagnosed Addison's disease.

Conclusion

S-cortisol is frequently analyzed and the most common cause of testing is evaluation or surveillance of patients already carefully cared for. A handful of patients however suffer from undiagnosed AI. If establishing a routine to alert clinicians on low S-cortisol levels, indication for the analysis should be marked in ordered to avoid unnecessary concern.

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P66

Evaluation of cardiometabolic profile of patients submitted to unilateral adrenalectomy

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Background and aims

It is known that unilateral adrenalectomy as treatment for autonomous secreting adrenal cortex adenomas effectively reduces cardiometabolic risk. Non-autonomous secreting adenomas are not expected to increase cardiometabolic risk, but this has not been thoroughly explored.We evaluated the blood pressure and glycemic profile before and after unilateral adrenalectomy for both autonomous and non-autonomous secreting adrenal cortex adenomas.

Patients and methods

This is a retrospective study of 30 consecutive patients submitted to unilateral adrenalectomy, assisted in a tertiary hospital.We evaluated systolic (SBP) and diastolic (DBP) arterial blood pressure, fasting glycemia,sodium (Na), potassium (K) and number of anti-hypertensive and anti-diabetic agents, 6 months before and after undergoing unilateral adrenalectomy for both secretory and non-secretory adrenal cortex adenomas.

Results

Patients' mean age was 55 $\pm$ 13 (21–77) years old and 70% were female. 9 (30%) had a cortisol or aldosterone secreting adenoma documented before surgery. Overall, mean tumor's maximum diameter was 29 $\pm$ 12 mm. 15 (50%) patients had hypertension and 3 (10%) were diagnosed with diabetes mellitus before surgery,requiring a mean of 1.2 $\pm$ 0.3 anti-hypertensive drugs and 0.3 $\pm$ 0.7 anti-diabetic agents per patient. After surgery, there was a significant reduction of the SBP (148 $\pm$ 21–123 $\pm$ 10 mmHg, $P=0.001$) and DBP(92 $\pm$ 16–78 $\pm$ 8 mmHg, $P=0.006$), an increase in serum potassium levels (4.1 $\pm$ 0.5–4.5 $\pm$ 0.6 mEq/l, $P=0.015$), a decrease in the number of anti-hypertensive agents (2.3 $\pm$ 1.4 to 1.3 $\pm$ 1.3 agents, $P=0.008$) and a decrease in fasting glycemia (121 $\pm$ 50–101 $\pm$ 31 mg/dL, $P=0.02$). Considering non-secretory adenomas separately, there was still a significant reduction of the SBP (147 $\pm$ 26 mmHg to 122 $\pm$ 11 mmHg, $P=0.022$), an increase in K levels (4.0 $\pm$ 0.4 mEq/l to 4.6 $\pm$ 0.6 mEq/l, $P=0.006$) and a trend towards less anti-hypertensive agents (2.1 $\pm$ 1.3 to 1.4 $\pm$ 1.4 agents, $P=0.054$). For patients with secreting adenomas there was a significant reduction in SBP ($P=0.018$) and DBP ($P=0.02$) and a trend to a lower fasting glycemia ($P=0.092$) after surgery.

Discussion

As expected, cardiometabolic profile improved in patients submitted to adrenalectomy for autonomous secreting adrenal adenomas.Notably, whatever the underlying mechanism,we also found an improvement in SBP and less need for anti-hypertensive agents after adrenalectomy for adenomas previously classified as non-autonomous secreting by clinical and biochemical evaluation.As a result, in both secreting and non-secreting tumors there was an improvement in cardiometabolic profile, which may improve long time cardiovascular outcomes.

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P67

Adrenal venous sampling in patients with ACTH-independent Cushing's syndrome

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Background

ACTH-independent Cushing syndrome (CS) accounts for 15–20% of endogenous CS. Approximately 10% of these patients have bilateral adrenal lesions where the differential diagnoses are primary bilateral adrenal macronodular hyperplasia (PBMAH), primary pigmented nodular adrenal disease (PPNAD), bilateral cortisol producing adenomas or a unilateral cortisol producing adenoma with a contralateral nonfunctioning adenoma. Also, the prevalence of subclinical CS is high in patients with bilateral incidentalomas. Management of these patients is challenging since the distinction between functioning and non-functioning adrenal masses cannot be determined by imaging. Adrenal venous sampling is the "gold standard" for distinguishing unilateral from bilateral aldosterone production. The role of the adrenal venous sampling (AVS) in patients with ACTH independent CS and bilateral adrenal lesions or normal adrenal glands is still not determined.

Methods

This was a retrospective analysis of 11 consecutive patients evaluated for ACTH-independent CS who were subjected to AVS at our institution between 2009 and 2017.

Results

Eight patients were referred for evaluation of bilateral adrenal incidentalomas, five of whom had subclinical CS and three overt CS. Three additional patients were referred due to overt CS. Thus, in total six patients had overt CS. Overt Cushing's syndrome: three patients had bilateral adrenal lesions. One of them had a unilateral dominant cortisol production and underwent left adrenalectomy. Two patients had bilateral cortisol production. One of them underwent bilateral adrenalectomy and histopathological diagnosis showed PBMAH. The other patient had a mild CS and was treated medically. Two patients had normal adrenal glands and bilateral cortisol production on AVS. Both underwent bilateral adrenalectomy and the histopathological examination showed PPNAD. The last patient, after extensive investigation, did not have ACTH-independent CS, but cyclic Cushing's disease. Subclinical CS: all patients had bilateral adrenal lesions. One patient had unilateral dominant cortisol production underwent unilateral adrenalectomy and developed adrenal insufficiency. The histopathological diagnosis was benign adrenal adenoma.

Conclusion

AVS distinctly contributed to appropriate choice of treatment in two of 11 patients. The role of AVS is limited in patients with CS, but may in some cases assist in the management decision of patients with ACTH independent CS and bilateral adrenal lesions or normal adrenal glands.

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P68

Association of the *Bcl*I glucocorticoid receptor polymorphism with metabolic parameters in female patients with adrenal incidentalomas

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Interindividual variations in tissue sensitivity to glucocorticoids have been partly attributed to polymorphisms in the glucocorticoid receptor (GR) gene. The aim of this study was to investigate the prevalence of subclinical hypercortisolism (SH) in women with adrenal incidentaloma (AI), and whether *Bcl*I variant of the GR gene may contribute to metabolic abnormalities frequently present in these patients. We evaluated 106 women with AI. Anthropometric characteristics included BMI, waist and hip circumference. SH was diagnosed in the presence of serum cortisol levels after 2-day low-dose dexamethasone suppression test (LDDST) >50 nmol/l with at least one of the following parameter (midnight serum cortisol >208 nmol/L, 24-h urinary free cortisol (UFC) >245 nmol/24 h, or adrenocorticotropin (ACTH) $<$ 10 ng/l). Non-diabetic patients underwent an oral glucose tolerance test with 75 g glucose. Insulin resistance was assessed by homeostasis model assessment (HOMA-IR) index. DNA was obtained from peripheral blood leucocytes. The polymorphism was detected using PCR, RFLP and DNA sequencing. The overall prevalence of SH was 20.2%. Carriers of the larger C allele of *Bcl*I polymorphism had significantly less suppression of cortisol levels after 0.5 mg dexametasone (126.4 ± 111.4 vs 80.9 ± 75.7 nmol/l, $P=0.026$), indicating relative GC resistance. No difference was noted in midnight and post LDDST serum cortisol concentrations, UFC, and ACTH levels. The mean age, BMI, waist circumference and waist-to-hip ratio did not differ between carriers and non-carriers. Most patients had central obesity. The prevalence of hypertension and dyslipidemia occurred with similar frequency in both groups. There was no significant difference in mean values of systolic and diastolic blood pressure and HOMA-IR index. The presence of the BclI polymorphism was associated with a reduced prevalence of type 2 diabetes in carriers compared with wild type (9.1% vs 26%, $P=0.034$). We demonstrated that female carriers of the larger C allele of *Bcl*I polymorphism display relative glucocorticoid resistance of the hypothalamic-pituitary adrenal axis and peripheral tissue. This polymorphism has a protective role and reduces the risk of diabetes in patients with AI especially in a state od subtle cortisol excess.

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P69

Adrenocortical carcinoma in the experience of one clinical center

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Adrenocortical carcinoma (ACC) is a rare neoplasm with poor prognosis. Patients can present signs of hormone excess: virilisation, Cusging's syndrome or only enlarged abdominal mass. Incidentally ACC can be also detected in the ultrasonography. Some of 'non-hypersecretory' ACCs can produce non-bioactive hormones steroid precursors or not very big amount of them and sometimes patients present subclinical Cushing's symptoms. Surgery and adjuvant radio-therapy and chemotherapy with Mitotane is the treatment of choice. The aim of the study was to analyse clinical features, hormonal test results and prognosis in patients with secreting and non- secreting adrenal cancers.

Patients

The study group included 49 patients: 11 men and 38 women median age 68 year. Clinical examination, the imaging studies and hormonal assays were performed. Forty four patients underwent surgical treatment, five of them were qualified only to palliative treatment. Chemotherapy with Lysodren was administered in 39 patients.

Results

Secretory tumors were diagnosed in 23 cases and non-secretory in 26 cases. Twenty five patients are still alive and the median time of observation is 60 months (min 13 months, max 312 months). Nineteen patients of this group were classified as the 1-st or 2-nd stage and 14 were diagnosed as non-secretory tumors. Due to ACC progress 22 patients died during the time of observation, and two patient died due to surgical complications. The median time of observation in this group was 15,5 months (min. 1 month an max 192 months). In this group 12 patients were classified as 3-rd or 4-th stage and 12 patients were diagnosed as secretory tumors.

Conclusion

The poor prognostic factors in ACC are: size of tumor, presence of local and distant metastases and hormonal activity. Chemotherapy with Lysodren prolong life of patients, but is less effective in advanced disease.

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P70

Adrenocortical carcinoma: retrospective analysis of a series of clinical cases

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Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive tumour. At diagnosis 21% has metastasis. Even after complete surgical removal, patients are at risk of recurrence as late as 10-12 years. The 5-year survival rate of Stage I to IV (ENSAT 2008) is 82%, 61%, 50% and 13% respectively.

Objetive

To describe the epidemiological and clinical characteristics, as well as the evolution, treatments and overall survival of patients diagnosed with ACC.

Methods

We identified 41 cases of ACC in the archive of the Pathological Anatomy department in La Paz University Hospital-Madrid (1969–2017). We reviewed the medical records of 24 cases that were followed in the our center (1984–2017).

Results

Of the 41 cases, 9 were children (21.5%), 23 women (56.10%). The median age of the children was 4 years, (P25–P50: 2–6), the mean age of the adults was 49.9 years (s.d.: 14.08). Total mortality in children was 50% and in adults 59%. The main characteristics of the 24 cases followed in our hospital is shown in the Table. An Stage IV case with complete remission and survival of more than 10 years was identified. ENSAT stage at diagnosis was a statistically significant variable for overall survival; it was not significant for sex, age, secretory status neither mitotane therapy in our cohort.

Table 1

	Children	Adults
N	4(16%)	20 (83%)
Female	4 (100%)	12 (60%)
Age (years)	5.5 (1.8–9.0)	53 (36–62)
Smoking/Previous Smoking	0/0	9 (47%)/4(21%)
Left Location	3 (75%)	8 (40%)
Secretory Tumor	4(100%)	10 (50%)
Cortisol	0	3
Androgens	4	3
Cortisol and Androgens	0	3
Aldosterone	0	1
ENSAT Stage at Diagnosis		
I	1 (25%)	6 (32%)
II	3 (75%)	10 (53%)
III	0	1 (5%)
IV	0	2 (10%)
ENSAT Stage at follow-up		
I	1 (25%)	5 (25%)
II	1 (25)	4 (20%)
III	0	2 (10%)
IV	2 (50%)	9 (45%)
Surgery Approach		
Laparoscopic	0	2 (10%)
Laparotomy	3 (75%)	16 (80%)
No surgery	1 (25%)	2 (10%)
Chemotherapy	1 (25%)	8(42%)
Radiotherapy	4%	0
Mitotane treatment	2 (50%)	10 (50%)
Recurrent Disease	1(25%)	7 (42%)
Survival		
1-year	2 (50%)	17 (85%)
5-year	2 (50%)	9 (45%)
10-year	2 (50%)	7 (35%)

Conclusions

Due to its infrequency, we believe that the epidemiological registry and the results of the different therapeutic approaches are convenient for a better treatment of this pathology.

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Adrenal medulla

P71

Imaging characteristics of pheochromocytomas

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Introduction
Pheochromocytomas are uncommon neuroendocrine tumors arising from chromaffin cells of the adrenal medulla. The aim of our study was to assess imaging characteristics of pheochromocytomas.
Methods
The study was a retrospective analysis of 23 patients with pheochromocytomas. All participants had a computed tomography scan (CT). Several clinical and radiologic features were statistically analysed.
Results
The Mean age was 47.04 ± 12.31 years and the sex-ratio (M/F) was 0.39. All pheochromocytomas were unilateral. Malignancy was proven in five cases. The mean tumor size was 54.17 ± 29.47 mm (Extremes: 20–130 mm). Out of 23 participants, 19 patients had a tumour larger than 30 mm. There was no significant correlation between tumour size and urinary metanephrines ($P = 0.8$). However, a significant correlation between tumor size and the degree of malignancy ($r = 0.54$, $P = 0.03$) was identified. The majority of pheochromocytomas ($n = 22$) had attenuation values greater than 10 Hounsfield units with a heterogeneous enhancement in contrast-enhanced CT. Smaller lesions were typically homogeneous (3/4) whereas larger tumours were more heterogeneous (16/19). Calcifications, necrosis and cystic components were present in 3, 8 and 2 cases, respectively.
Conclusion
Computed tomography scan has been established as the main tool to identify pheochromocytoma, with an overall sensitivity of 89%. The typical appearance of a pheochromocytoma in computed tomography is a mass with a large size, high density greater than 10 Hounsfield units, avid contrast enhancement due to a rich capillary network, and delayed washout. Cystic changes, necrosis, and internal calcifications are commonly described in the literature.

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P72

Genetics in pheochromocytoma and paraganglioma: a case series

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Introduction
In most patients with familial history of pheochromocytoma/paraganglioma, leads in the majorty of cases to a postive genetic testing for mutations, and what's more in those patients with no familial antecedents, about 10–25% carry a mutation in one related gene. In these cases other aspects like, bilaterality, multiplicity or location must be taken into account.
Objective
The objective of the study was to discuss the importance of genetic testing in apparently sporadic cases.
Design
Nine probands, with no familial or personal antecedents of pheochromocytoma or paraganglioma, were analyzed for the major genes: VHL, RET, SDHB, SDHC and SDHD.
Results
Nine probands (six men and three women) with an average of 55.8 ± 10.3 years old were analyzed, 8 cases (88.8%) of pheochromocytoma and only one proband with non-fuctioning paragangliomas (mediastinal paraganglioma and glomus jugulare tumor). Genetic analysis was performed using a multi-gene panel testing for the major genes, for analyzing patients' blood and tumor samples. A rate of 33.3% for genetic mutations was found: RET (C634S) (1 of 9) and SDHD (c.242C > T (p.Pro81Leu)) (1 of 9), VHL (pVal84/Met) (1 of 9), in this last case no mutations were found on blood sample but the mutation for VHL was found in paraffin embedded sample. In our serie, genetic testing was performed on first grade relatives of patients affected, being diagnosed two first grade relatives of mutations during the study: one for VHL mutation and one for RET mutation, in this last case, with initial diagnosis of medullary thyroid cancer and development of pheochromocytoma in a five year follow-up interval.
Conclusions
We recommend genetic testing in all patients, not only in those with familial antecedents but also in sporadic tumors, regardless of age or location (In our serie 80% were unilateral adrenal masses, 10% bilateral masses and 10% extraadrenal location). We emphasise the importance of genetic testing in first grade relatives, as in our serie, in 22% of probands affected of pheochromocytoma/paraganglioma, at least one first grade relative was carrier of the mutation.
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P73

Analysis of a pheochromocytoma case series over 12 years: a specialty hospital experience

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Introduction
Pheochromocytomas are the most common tumours of adrenal medullary origin. The aim of this study is to describe the clinical manifestations, biochemical profile, preoperative pharmacological approach and hemodinamic outcomes in a series of patients with histologically proven pheochromocytoma treated in our center over 12 years.
Methods/design
Descriptive analysis including patients diagnosed with pheochromocytoma after histological examination. Patients with suspected tumour without histological evidence were excluded for assesment as well as those whose medical records were incomplete.
Results
Pheochromocytoma was histologically diagnosed in 11 out of 15 patients from 2002 to 2014. One patient was excluded because of incomplete medical records. There were 6 females and 5 males (F:M = 1.2:1), age ranged from 27 to 80 years. Presenting form was persistent and/or refractory hypertension in 2 patients, incidental adrenal mass in 2 cases and paroxysmal hypertension crisis in 5. Two cases presented as abrupt hypertensive emergency. The most common clinical manifestations were headache (7 cases), palpitations (6 cases) and perspiration (5 patients). Type of tumour secretion: norepinephrine (5), norepinephrine and epinephrine (4), norepinephrine, epinephrine and dopamine (2). All patients underwent successful surgical removement and unilateral adrenal mass was identified in all cases (left gland in 8 cases). Median mass size was 3 (range: 1.5–10) cm. Preoperative selective alfa-blockade was performed with phenoxybenzamine in 7 cases and 4 patients received non-selective alfa-blockade with doxazosin. Beta-blockade was needed in 9 cases. Preoperative systolic blood pressure: 130 (120–140 mm Hg), diastolic blood pressure 80 (71.2–87.5 mm Hg) and heart rate: 71 (65–85 bpm). Mean time until optimal pharmacological blockade: 21 days.
Conclusions
There were no classic presenting form for pheochromocytoma in our series, although clinical history and physical findings are helpful. There wasn't any standard approach in preoperative pharmacological blockade. Though therapeutic results were favourable, protocols for preoperative management may be considered in our center.

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Laparoscopic surgery for pheochromocytoma: perioperative outcomes

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Introduction
Laparoscopic adrenalectomy is a promising alternative to open surgery although concerns exist in regard to laparoscopic treatment of pheocromocytoma. This report aims to describe the outcomes of laparoscopic resection for pheocromocytoma focusing particularly on intraoperative hemodynamic stability and postoperative outcomes.
Methods/design
Descriptive analysis including patients who underwent laparoscopic surgery for unilateral pheochromocytoma in our center. Patients who required emergency surgery were excluded from analysis, so every patient received previous alfa and beta blockade. Patients who didn't meet Roizen's criteria before surgery and patients with bilateral tumours or paraganglioma were also excluded. Intraoperative hemodynamic stability including need of vasoactive drugs was studied. Postoperative complications and length of stay from post-anesthesia or intensive care unit admission to discharge to conventional medical ward, were

recorded. Quantitative variables are described as median (range) or number of cases in which some particular clinical conditions were observed.
Results
Ten patients were included (six women, five men; median age: 53 (27–80) years. Median size of tumour: 2.8 (1.5–10) cm. Type of tumour secretion: norepinephrine (4), norepinephrine and epinephrine (4), norepinephrine, epinephrine and dopamine (2). Preoperative systolic blood pressure: 130 (120–140) mm Hg, diastolic blood pressure 80 (71.2–87.5) mm Hg and heart rate: 71 (65–85) bpm. All tumours were successfully removed. One laparoscopic procedure were converted to open procedure due to large mass size (above 10 cm). Intraoperative results: median operative time was 150 (90–180) min, median blood pressure was 92.5 (85–100) mm Hg, hypertensive crisis requiring use of vasoactive drugs and hypotensive crisis requiring volumen expanders were documented in 4 and 3 cases, respectively. No arrythmias were documented. Postoperative results: treatment for transient hypertension was needed in 2 cases, 2 patients suffered from hypoventilation and hypotension was found in 2. Median time from post-anesthesia/intensive care unit to discharge to conventional hospital ward: 48 (24–96) hours. Laparoscopic adrenalectomy was effective in normalization of endocrine profile in all cases.
Conclusions
Laparoscopic resection of pheochromocytomas can be accomplished safely by experienced surgeons. A short operative and post-anesthesia care wards stay with minimal intra and postoperative hemodynamic inestability coupled with eradication of endocrinopathy support the minimally invasive approach for adrenalectomy in the setting of pheochromocytoma.

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Malignant pheochromocytoma discovered upon consultation for painful erections

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Introduction
Pheochromocytomas (PCCs) and paragangliomas (PGL) are rare but unique tumors. Only 10% of PCCs are malignant, defined by metastases. Metastases can be seen at diagnosis of the primary tumor or develop even 20 years later. Approximately half of patients with metastatic PCC/PGL have inherited SDHB mutations.
Case report
A 45-year-old man was referred to Urology for curvature of the penis and painful erections. Among his medical background highlighted high blood pressure and herniated disc intervened twice. Abdominal US revealed a large heterogeneous lesion in the right suprarenal region. A CT scan of the abdomen revealed a 9x5.8x6.1 cm heterogeneous right suprarenal mass. Laboratory analysis showed elevations in urine fractionates metanephrines (771 mg/24 h [25–312]) and normetanephrines (1425 mg/24 h [35–445]) levels. $^{1\text{-}123}$ MIBG scintigraphy revealed uptake in the right adrenal region. Two months after diagnosis blood pressure figures were raised, being difficult to control.Phenoxybenzamine was used for preoperative preparation prior to surgical resection. Nephrectomy and right adrenalectomy were performed. Histopathology confirmed pheochromocytoma with lymph nodes metastasis. At six months follow-up, 4 right retrocrural lymph nodes metastasis of 7–10 mm were detected in CT scan and confirmed by 18F-dopa PET. $^{1\text{-}123}$ MIBG scintigraphy did not reveal any uptake. Surgery was performed by high right para-aortic lymphadenectomy. Histopathological examination confirmed the diagnosis of pheochromocytoma metastasis in three nodes. Six months after surgery a follow-up 18F-dopa PET/TAC detected a 8-mm right retrocrural lymphatic metastasis with a maxSUV of 2.8. Catecholamines and metanephrines levels were within the normal range and blood pressure was controlled with enalapril. The genetic study performed in peripheral blood (SDHB) and tumor piece (SDHB, SDHC, SDHD, SDHA, SDHAF1, SDHAF2, RET, MEN-1, VHL, NF1, KIF1, BETA, MAX, TMEM127, MDH2, FH, EPAS1, HRAS) did not show genetic alterations. A 18F-dopa PET/TAC performed 4 years after the first surgery detected a retrocrural lymph node metastasis of 3 mm with a maxSUV of 2.2.
Conclusion
Complete resection is the only curative treatment in metastatic disease. Given the often indolent nature of the disease, other therapies (mainly 131I-MIBG, chemotherapy and/or radiation) are reserved for patients with severe symptoms or clear progression. A wait and see policy is recommended as first-line management in asymptomatic patients. The management of these patients requires a multidisciplinary follow up. Eventually a better knowledge about genetics might lead us to find better targets for therapy.

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Can patients with a large sporadic pheochromocytoma and very high norepinephrine secretion be normotensive? Yes, they can!

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Introduction
Classically, hypertension (sustained or paroxysmal) is described in > 98% of diagnosed pheochromocytomas. Nowadays the systematic workup of adrenal incidentalomas has made uncovering normotensive pheochromocytomas no longer exceptional. However, normotensive pheochromocytomas have a catecholamine secretion characteristically lower than hypertensive pheochromocytomas. It must be emphasized that the perioperative hemodynamic instability is comparable in hypertensive and normotensive pheochromocytomas, and much higher than in non-pheochromocytoma adrenal masses.
Clinical case
After caustic ingestion, a 53-year-old male patient suffered extensive gastric ulcers and pyloric stenosis. He was referred to our Endocrinology Clinic because in a CT scan a dense heterogeneous mass measuring 4.4x4.6 cm with gross calcifications and lobulated outline was incidentally found in the right adrenal. The patient was asymptomatic, normotensive, had no medication except pantoprazol, and reported no history of hypokalemia, headaches or hypertensive crisis. The physical exam was unremarkable, with height 179 cm, weight 73 kg, BP 126/81 mmHg, HR 68 lpm. There were no signs of Cushing's syndrome. Glucose, creatinine and eGFR, ions, lipids, transaminases, GGT, blood count, TSH, cortisol, ACTH, LH, FSH and testosterone were normal. Fasting cortisol was 14.4 µg/dL, aldosterone 10.3 ng/dl, PRA 1.1 ng/ml/h, ratio A/PRA 9.4 (normal). Unexpectedly, plasma metanephrine was 35 pg/ml (normal), normetanephrine 2264 pg/ml (UNL 196), and cromogranin A 361.5 ng/ml (UNL 100) with 24 h urinary metanephrine 264 µg (normal) and normetanephrine 1656 µg (UNL 444). A MIBG/SPECT CT scan showed a right adrenal pheocromocytoma without additional lesions. 24 h ABPM was performed in order to confirm normotension. Awake BP was 128/75 mmHg with HR 81 lpm, sleep BP was 115/64 mmHg with HR 69 lpm, with normal dipper pattern, but there was an unexplained BP peak (159/84 mmHg) at 16:00. The patient is at present ready for right laparoscopic adrenectomy, having started treatment with doxazosin 4 mg bid followed by bisoprolol 10 mg bid, adequate hydration and ClNa supplements 6 g/24 h, with mild hypotensive symptoms.
Conclusions
We certainly would expect a patient with such a large epinephrine output to be hypertensive, but have no explanation why it was not the case. The workup of adrenal incidentalomas must include screening for pheochromocytoma even in normotensive patients. In order to prevent perioperative hemodynamic instability, patients with normotensive or hypertensive pheochromocytoma need the same preparation (including adrenergic blockade, hydration and salt supplementation) although it might elicit symptomatic hypotension.

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P77

Pheochromocytoma revelation modalities: about 23 cases

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Introduction
Pheochromocytoma is an endocrine tumor developed in the chromaffin cells of the adrenal medulla and excessively secreting catecholamines in varying amounts and types. It represents a rare tumor, often benign, but serious considering its mainly cardiovascular complications. The purpose of our study is to specify the revelation methods of pheochromocytomas in our population.
Patients and methods
Our study has included 23 cases of pheochromocytomas followed in the endocrinology department of the Mohammed VI University Hospital of Marrakech between 2012 and 2017.

Results
The mean age of patients was 42.4 years, the sex ratio was 1.8 with female predominance. The circumstances of discovery were a triad of Menard in 69% of cases, an HTA in 43% including 2 cases of pre-eclampsia, an adrenal incidentaloma in 26%, an acute coronary syndrome in 2 cases, a transient ischemic attack in one case, a subocclusive syndrome in 1 case and during a histological examination of an operative specimen in 1 case. The most frequent location was on the right (50% of cases) with 4 cases of bilateral incidentaloma, the average size was 67 mm.
Discussion
Pheochromocytoma is a rare tumor whose variable clinical expression is dominated by the Menard triad and hypertension but which can be revealed by an acute array, surgical treatment is the only curative treatment but remains limited for malignant forms.

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P78

When the large tumor is not the first intention for removal-concomitant discovery of left adrenal pheochromocytoma and a possible retroperitoneal plexiform neurofibroma in a case of familial neurofibromatosis type 1- case report

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Neurofibromatosis type 1 (NF1) is a rare autosomal dominant disorder characterized by the development of multiple benign tumors of the nerves and the skin (neurofibromas) and areas of abnormal increased and decreased coloration of the skin. Pheochromocytoma develops in 0.1–5.7% of NF1 patients and plexiform neurofibroma in 30% of NF1 patients. We present a case of a 38-year-old female, without relevant personal, with a familial phenotype suggestive for NF1, evaluated for a two years history of tachycardia and hypertension. The clinical examination meet the criteria for NF-1 (skin tags with cutaneous and subcutaneous neurofibromas, café-au-lait spots and axillary freckling and Lisch nodules revealed in the ophthalmologic examination). She is the mother of two daughters, one of them with severe scoliosis. Laboratory testing showed pure autonomous adrenergic secretion with more than three times plasma metanephrine and normal normetanephrine. The abdominal MRI described a left adrenal mass of 22/21 mm and an inhomogeneous hypointense mass 62/42/49 mm that rises from the neural plexus situated between the right kidney psoas muscle and the posterior abdominal wall with central contrast enhancement suggestive of a plexiform neurofibroma. We performed removal of the left adrenal pheochromocytoma after alpha-adrenergic blockade. Following surgery, the patient had normalized the blood pressure and had normal range plasma metanephrine. Elective surgery for the abdominal plexiform neurofibroma is planned because of his malignant potential.

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P79

Why is it important to screen secondary endocrine hypertension in resistant cases? Lessons from a patient with progressive renal failure

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Introduction
Even though most hypertensive patients have essential hypertension, in the resistant cases the prevalence of secondary hypertension is much higher; therefore its screening should be mandatory. Resistant hypertension usually causes a progressive decline of renal function if blood pressure is not adequately controlled. Such decline is often irreversible; however a timely diagnosis leading to a resolutive treatment can alleviate or even revert the progression of the renal disease.
Clinical case
A 66 year old woman had been diagnosed of essential hypertension when she was 49 years old. She was treated with a combination of Fosinopril, Telmisartan, Amlodipine and Hydrochlorothiazide but her blood pressure was usually $>160/100$ mmHg; she had nephrotic syndrome with proteinuria >5 g/24 h and her eGFR was deteriorating (83 ml/min/1.73 m^2 in 2013, 40 ml/min/1.73 m^2 in April 2017). After complaining of abdominal pain, she was diagnosed of sigmoid adenocarcinoma, and underwent successful surgical rejection. In the presurgical workup, an incidental mass measuring 4.3x1.7 cm was found on top of the left adrenal in a CT scan, and she was referred to our Endocrinology Clinic. Lab tests showed metanephrin 117 pg/ml, normetanephrin 1464 pg/ml and cromogranin A 159.9 ng/ml. A MIBG/SPECT CT showed isolated hypercaptation next to the left adrenal. After adequate preparation, on 25/04/2017 a 4.3-cm mass was resected along with the adjacent left adrenal, which was normal. The final pathology diagnosis was paraganglioma (KI-67 negative, cromogranin A positive) without extracapsular extension. One month after surgery the patient was asymptomatic with normal blood pressure (113/67 mmHg) under treatment only with Manidipine 10 mg/day. The eGFR has improved (60 ml/min/1.73 m^2), albuminuria had decreased dramatically (232 mg/24 h) and cromogranin A and metanephrines were normal.
Conclusions
This case illustrates the importance of the etiologic diagnosis and treatment in secondary resistant hypertension. The patient was relentlessly progressing to end-stage renal failure but presently her blood pressure is well controlled while minimally treated, and her renal function has markedly improved.

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P80

Association of pheochromocytoma and neurofibrematosis type1: about 4 cases

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Introduction
Pheochromocytoma is rarely associated with neurofibromatosis type 1 (NF1). We report 4 observations of hospitalized patients in theIbn Rochd University Hospital endocrinology department in Casablanca.
Observation 1
A 52-year-old male patient was admitted for NF1-associated malignant pheochromocytomawith paroxysmal hypertension, Menard triad, elevated methoxylated urinary derivatives (DMU), and 11 * 8 cm right adrenal mass with hepatic metastasis. A surgical excision of the mass was performed with death of the patient following a hemorrhagic shock.
Observation 2
A 62-year-old patient was admitted for bilateral pheochromocytoma associated with NF1. He had hypertension, Menard triad, and two right (10 * 9 * 8 cm) and left (2 cm) adrenal masses, with no extra-adrenal localization. Bilateral adrenalectomy was performed. Pathological study showed a right pheochromocytoma complete excision with left adrenal hyperplasia. We rated a persistence of a moderate hypertension.
Observation 3
A 26-year-old patient, was operated 4 times for a face shwanoma, was admitted for pheochromocytoma associated with NF1. He had hypertension without menard triad, raised DMU, and left adrenal mass of 3 cm. He died 1 month later by cerebral involvement.
Observation 4
A 22-year-old patient was admitted for pheochromocytoma associated with NF1 discovered by incomplete Menard triad, elevated DMU, right adrenal mass (68 × 80 mm) including IVC in its inferior vena cava retrohepatic portion. Patient did not receive a surgical excision.
Discussion
Our observations illustrate the need to look for pheochromocytoma in any patient with NF1 because of its serious consequences.

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P81

A retrospective audit on the peri-operative management of phaeochromocytomas: "Phenoxybenzamine or Doxazosin"?

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Phaeochromocytomas are rare catecholamine secreting tumours with an incidence of 1:4500–1:1700 in the United States. Doxazosin and Phenoxybenzamine are alpha-1 selective and non-selective alpha blockers respectively which are commonly used to treat this condition peri-operatively. There are no randomized controlled studies comparing the effectiveness of these two medications. However, there are retrospective studies comparing these two medications; some favouring alpha-1 selective blockade and some showing no difference.

Aim:

To compare and contrast the effectiveness of Phenoxybenzamine and Doxazosin in treating phaeochromocytomas at our centre.

Methods:

Retrospective data collection of phaeochromocytomas, identified from elevated urinary metanephrines from the laboratory and coding for adrenalectomies over a five year period.

Results:

12 out of 171 patients with elevated urinary metanephrines had confirmed, 11 phaeochromocytomas and 1 paraganglioma. 11 out of 31 adrenalectomies performed were for phaeochromocytomas. Mean age of our cohort was 54 years, with 7 (58.3%) Males and 11 (91.6%) Caucasians. All patients were on beta blockers peri-operatively. In the Doxazosin group: $n=8$(66.7%), Mean pre-operative blood pressure (BP) = 128/80 mmHg, Mean intra-operative BP = 122/72 mmHg, Mean highest systolic and diastolic BP intra-operatively was 159 and 90 mmHg respectively, Mean length of surgery was 4 hours 15 minutes, Mean intra-operative fluids prescribed = 3.6 L, 4 patients(50%) were given other agents to control the BP intra-operatively ranging from 1 to 3 different agents. In the Phenoxybenzamine group: $n=4$(33.3%), Mean pre-operative BP = 121/73 mmHg, Mean intra-operative BP = 125/69 mmHg, Mean highest systolic and diastolic BP intra-operatively was 164 and 92 mmHg respectively, Mean length of surgery was 4 hours 40 minutes, Mean intra-operative fluids prescribed = 3.17 L, 1 patient(25%) was given 3 agents to control the BP intra-operatively.

Conclusion:

Doxazosin seems to be as effective as Phenoxybenzamine in the peri-operative management of this condition. Even though there were more patients in the Doxazosin group requiring other intra-operative agents to control the BP, it was not statistically significant ($\chi=0.6857$, $P=0.408$). Ideally, we need a bigger cohort to have the power to demonstrate the true significance of the differences between the two medications. There are a number of limitations in this audit, in particular, the sample size and the rarity of this condition. The experience of the anaesthetist could also be a contributing factor for the use of other agents intra-operatively.

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Calcium & Vitamin D metabolism

P82

25-OH vitamin D concentration and inflammation indicators in patients with non-functioning adrenal incidentalomas

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It is a well-known fact that vitamin D has an impact on many tissues of human body. Recent studies showed that vitamin D deficiency has an influence on inflamation indicators in several endocrine diseases (for example PCOS, graves disease). The aim of the study was to demonstrate correlation between 25-OH vitamin D concentration and chosen inflammation indicators (C-reactive protein and insulin) in patients with non-functioning adrenal incidentalomas. Seventy-one patients hospitalized in Endocrinology City Hospital in Piekary in 2015–2017 with non-functioning adrenal incidentalomas were included to the study. Exclusion criteria were adenomas producting hormones, vitamin D supplementation, liver or kidneys failure. Biochemical parameters (C-reactive protein, 25-OH vitamin D concentration, fasting glucose, insulin, HBA1C% and HOMA-IR) were obtained during routinely performed tests in the hospital and taken from the patient's medical record. Anthropometric parameters were measured in the morning hours, in light clothes. The results were used to calculate the anthropometric indicators (BMI, BAI, VAI, WHR, WHtR). The collected data were statisstically analyzed using the Statistica 12 ($P\leq0.05$). In the analyzed group mean concentration of 25-OH vitamin D was 20 ± 8.4 ng/dl, fasting glucose 111.5 ± 29.8 mg/dl, insulin 13.2 ± 7.9 uU/mL, HBA1C% 6.1 ± 0.7, HOMA-IR 3.8 ± 2.9, CRP 2.8 ± 1.1. Insulin concentration correlated possitively ($P\leq0.05$) with BMI ($r=0.46$), BAI ($r=0.21$), WHR ($r=0.12$), WHtR ($r=0.42$). CRP was statistically higher ($P\leq0.05$) in patients with higher BMI ($r=0.13$), WHR ($r=0.07$), WHtR ($r=0.10$). There was no signifficant correlation ($P>0.05$) demonstrated neither between 25-OH vitamin D and CRP nor 25-OH vitamin D and insulin. The study indicates that the measurement of anthropometric parameters (BMI, BAI, WHR and WHtR) could reflect CRP and insulin concentration in the analyzed group with non-functioning adrenal incidentalomas. Vitamin D concentration in the studied group of patients does not demonstrate correlation with chosen inflammatory indicators. It is worth to enlarge studied group to confirm obtained results.

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Cardiovascular Endocrinology and Lipid Metabolism

P83

Arterial hypertension from the adrenal gland: Prognosis and predictive factors of recovery after chirurgical treatment

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Background

Arterial Hypertension from the adrenal gland accounts for approximately 3% of diagnosed hypertension. The long-term surgical cure rate of patients with adrenal hypertension varies widely and causes of persistent hypertension are not completely established. The Aim of our study was to assess the prognosis of arterial hypertension from the adrenal gland and to determine its recovery predictive factors.

Methods

It was a retrospective, descriptive and analytical study including 67 patients with arterial hypertension from the adrenal gland (29 patients with primary hyperaldosteronism (group 1), 27 patients with pheochromocytoma (group 2) and 11 patients with Cushing's syndrome (group 3)). Adrenalectomy was performed in all patients. Clinical and paraclinical data were determined before and after surgery. Hypertension recovery was defined by a blood pressure $<140/90$ mmHg without any antihypertensive drugs. Predictors of recovery were determined by calculating Odds Ratios.

Results

After adrenalectomy, a significant decrease in blood pressure was obtained in all three groups. The cure rate for hypertension was 52% in group 1, 37% in group 2, and 55% in group 3. Clinical and paraclinical profiles of patients recovered were comparable to those not cured in patients groups 1 and 3. In contrast, in group 2, cured patients had a lower prevalence of diabetes ($P=0.026$), a lower duration of hypertension ($P=0.003$), a lower LDL-cholesterol level ($P=0.022$), a higher creatinine level ($P=0.020$) and a lower prevalence of renal failure ($P=0.049$). For groups 1 and 3, we did not find any significant associations between recovery of hypertension and the most studied predictive factors in the literature, namely, young age, absence of family history of hypertension, duration of hypertension less than 5 years and the absence of overweight. However in group 2, the chances of curing hypertension were significantly multiplied by 10.1 in the absence of diabetes, by 8 in the absence of renal insufficiency and by 4.5 in the case of hypertension duration less than 5 years.

Conclusion

The persistence of hypertension after adrenalectomy could be the result of reduced ability to reverse pathological changes in the blood vessels or coexisting essential hypertension. Therefore, early screening and diagnosis, adequate hypertension control before surgery and management of associated comorbidities are mandatory in order to improve patients' outcome.

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P84

Metabolic and hormonal profile in primary aldosteronism as compared with essential hypertension

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Background
Primary aldosteronism is associated with increased vascular mortality and morbidity.
Aims
We aimed to assess metabolic and hormonal profile differences in patients with primary aldosteronism (PA) compared with patients with essential hypertension (EH).
Patients and methods
Thirty-one patients (11 M/20 F) with primary aldosteronism, aged 46.2 ± 12.9 years and 64 patients (24 M/40 F) with essential hypertension, aged 40.9 ± 13 years, were retrospectively reviewed. Plasma aldosterone and plasma direct renin were measured by chemiluminescence (CLIA).
Results
Systolic blood pressure was significantly higher in PA patients (214.1 ± 27.5 mmHg) than in patients with EH (197.8 ± 29 mmHg), $P = 0.02$, while diastolic blood pressure was similar. Body mass index tended to be higher in patients with EH (29.9 ± 6.4 kg/m^2) than in PA patients (27.8 ± 1.1 kg/m^2), $P = 0.07$. Serum fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were similar between the two groups. PA patients had higher median midnight serum cortisol (4.3 μg/dl vs 1.83 μg/dl, $P = 0.057$), significantly higher median 0800 hrs. serum plasma cortisol after 1 mg dexamethasone suppression test (1.34 μg/dL vs 0.8 μg/dL, $P = 0.01$) and plasma metanephrines (50.4 pg/ml vs 29.4 pg/ml, $P = 0.048$) than patients with EH. Serum PTH levels were significantly higher in patients with PA (76.6 ± 23.7 pg/ml) than in patients with EH (46.7 ± 17.9 pg/ml), $P = 0.02$, while 25 OH vitamin D levels were similar.
Conclusion
PA patients showed a more severe systolic hypertension, with similar metabolic profile and an adverse hormonal profile with a slight cortisol and PTH excess.

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P85

Aortic root dilatation in primary aldosteronism: is treatment effective in reducing aortic damage?

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Introduction
Cardiovascular morbidity is more prevalent in primary aldosteronism (PA) than in essential hypertension. Preclinical studies have shown a possible association between ascending aorta dilatation and PA, probably mediated by the mineralocorticoid receptor.
Patients and methods
A total of 84 patients attending the Endocrinology Unit of the S. Orsola-Malpighi University Hospital of Bologna, (Italy) were evaluated. Thirty-nine patients had a diagnosis of PA. The control group (NS) consisted of 45 hypertensive patients with an adrenal adenoma or hyperplasia, in whom primary aldosteronism, hypercortisolism and pheocromocytoma were appropriately excluded. All patients underwent transthoracic echocardiographic assessment at baseline. Ten PA patients underwent adrenalectomy due to unilateral adrenal disease, whereas the remaining 29 PA subjects were treated with a mineralocorticoid receptor antagonist. The aortic root was measured on each echocardiographic assessment. PA patients underwent a further echocardiographic evaluation during follow-up.
Results
PA and NS groups were homogeneous as to age and body surface area. The aortic root was significantly higher at baseline in PA group as compared with NS group (34.9 ± 5.3 mm vs 32.2 ± 3.9 mm, $P < 0.01$). Age was significantly different between the surgically treated and medically treated PA patients (47.7 ± 9.1 years vs 57.1 ± 9.9 years respectively, $P = 0.01$). In PA group, the mean duration of follow-up was 4.2 ± 2.3 years. Within the surgically treated PA, the aortic root measured 34.9 ± 5.3 mm before adrenalectomy and 33.9 ± 4.9 mm at follow-up ($P = 0.47$). In the medically treated PA group, the aortic root measured 34.6 ± 4.7 mm at baseline and 35.1 ± 4.8 mm at follow-up ($P = 0.94$). Also, percentage variation did not show statistical significance in either group.
Conclusion
PA patients showed larger aortic roots as compared with a homogeneous hypertensive population. Our preliminary follow-up data suggest that treatment of primary aldosteronism might not reverse vascular damage, thus suggesting a pathogenesis of irreversible vascular fibrosis induced by aldosterone excess.

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Clinical case reports - Pituitary/Adrenal

P86

Abstract withdrawn.

P87

Long-term follow-up of congenital adrenal hyperplasia due to 11β-hydroxylase deficiency

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Introduction
Congenital adrenal hyperplasia (CAH) due to an enzymatic defect in 11-beta-hydroxylase (11β-OHD) is the second most common cause of CAH representing 5-8% of cases. It is characterized by androgen excess, hypertension and hypokalemia. Here we describe the case of a patient having a CYP11B1 mutation and being followed-up during 33 years.
Observation
A 36-year-old Tunisian male was diagnosed with 11β-OHD at the age of three years revealed by precocious pseudopuberty. Laboratory findings was characterized by high serum concentrations of 11-deoxycortisol (656 nmol/l), high ACTH level (1500 pg/ml) and low plasma renin activity (0.7 ng/ml). A homozygous p.G379V mutation in exon 7 of the CYP11B1 gene was found. The patient was issued from consanguineous marriage. He had three other family members having the same disease and all treated by hydrocortisone. He had two healthy children aging respectively of three and one-year-old. Acute adrenal deficiency didn't occur during the follow-up. Hypertension associated with hypokalemia was discovered 23 years later and treated by calcium channel blocker. It has been complicated only by hypertensive retinopathy grade 1. The patient had a metabolic syndrome. He had an android fat distribution (BMI = 31.5 kg/m^2 and 102 cm abdomen circumference), a height of 169 cm, a normal external genitalia examination and bone density. The patient had normal glucose and triglyceride level with hypoHDLemia (0.23 g/l).
Discussion
CAH is an inherited autosomal recessive genetic endocrine disease. It is a group of diseases resulting from the deficiency of one of the steroidogenesis enzymes. 21-hydroxylase deficiency is the most common followed by 11β-OHD. In 11β-OHD, the p.G379V mutation found in our case in addition to the p.Q356X mutation have been described in Tunisian population. There is no systematic evaluation in adulthood of patients having 11β-OHD. Little is known regarding height, bone health, diabetes and mortality in those patients.

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Rhabdomyolysis in a case with severe hypokalemia and Primary Hyperaldosteronism

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Case Report
A 47 years old female was admitted to our hospital with muscle pain, weakness of the lower extremities, faligue, muscular cramps, nausea, anorexia and elevation of blood preasure. The muscular pain started 20 days ago and got worse over the last few days, she also had difficulty walking during these time. She denied fever, trauma history, vomiting, diarrhea and diuretic or statins use in the last days. The laboratory examinaition on admission showed severely low potassium values (1.4 mEq/L) and elevated values of creatine kinase, lactate dehydrogenase, troponin, myoglobin and aldosteron. Blood Gas Analysis revealed metabolic alkalosis.The patient had been under treatment for high blood pressure for more than six years, with ARBs and calcium channel blockers. Based on clinical, laboratory and imaging studies we suspected the diagnosis of of primary hyperaldosteronism associated with rhabdomyolysis due to severe hypokalemia as a cause was done. Treatment with I.V and oral hydration, Sol KCl and spironolactone was started. Our patient was wrongly diagnosed with essential high blood preassure. After admission to our hospital, we evaluated nad treated the patient, also prevented a potential acute renal failue from rhabdomyolysis and life-threatening arryhmias, and the diagnosis of Primary Hyperaldosteronism was made.

Keywords: Rhabdomyolysis, hypokalemia, CK, primary hyperaldosteronism.
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P89

Pheochromocytoma in young patient-challenges in clinical practice

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A pheochromocytoma is a rare, catecholamine-secreting tumor that may precipitate life-threatening hypertension. The tumor is malignant in 10% of cases. Although pheochromocytoma has classically been associated with von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN 2), and neurofibromatosis type 1 (NF1) there are now 10 genes that have been identified as sites of mutations leading to pheochromocytoma.
Method and materials A case report.
Results
We present a 27 years old patient with spontaneous hematoma of frontoparietal brain region. On digital subtraction angiography no vascular anomaly was detected. Intracerebral hematoma was in resorption in control with MRI. He had high blood pressure in several occasions, also he reported flushing in face during the physical activity and one to two mushy stools. During additional examination (ultrasonography and CT scan of abdomen) we found expansive mass in right suprarenal gland sized 70 mm, with postcontrast intensification. Chest X-ray was normal. Ultrasonography of thyroid showed nodule of 5 mm in right lobe. All day monitoring of blood pressure was in normal range. Examination of *fundus* of the *eye was normal. Echocardiographic ultrasound showed RVSP was* 28 mmHg, *tricuspid regurgitation 1+, and EDD of left ventricle 5.0 cm, ESD 3.3 cm and EF 63%. Immunological, hormonal status, plasma level of serotonin and tumor markers (NSE, CEA, CgA, calcitonin) were within normal range. Urinal catecholamine was repeated three times and was normal. Diurnal rhythm of cortisol was normal. Blood was taken for genetic analysis (VHL gene, TMEM, MLPA SDHx). Patient was prepared with* Phenoxybenzaminhydrochlorid and underwent surgery procedure. Histopathology tumor had 78 g sized 7×4.5 cm indicated it was Pheochromocytoma PASS 1/20 and immunohistochemically he was positive for CgA, Syn, S100, Ki67 < 0,1%. On the one year follow up abdominal MRI showed hyperplasia of left adrenal gland sized 20×13 mm. He still had episodes of high blood pressure and flushing. MIBG scintigraphy was normal. Hormonal and suppression test were normal. OGTT, tumor markers and catecholamine's were normal. Genetic study was negative for VHL MLPA and SDHx(B D C). TMEM and MAX (myc associated factor x) analysis are still in work. Scintigraphy of somatostatins receptors were normal. We preformed PET/CT with F18 DOPA, 231 MBq showed no signs of metabolic active disease.
Conclusion
In patients with spontaneous hematoma with no vascular anomaly, pheochromcytoma should be considered. Because of hyperplasia of left adrenal gland and undertaken analysis we decided for wait and watch

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P90

Opioid-induced secondary adrenal insufficiency

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Introduction
Opioids are commonly used for the treatment of pain, and their effects on the HPA (hypothalamic pituitary adrenal) axis may be under-recognised. In the present, a few non-systematic studies have investigated the effects of opioids on the HPA axis, but results have been conflicting. To our knowledge, there is only another case report of secondary adrenal insufficiency due to tramadol therapy, resulted in suppression on the HPA axis. We present the case of a 79 year old female who was referred to our clinic for endocrinological evaluation with a history of severe osteoporosis, treated with bisphosphonates and tramadol. At the referral, the patient was in mild distress due to the pain, with severe skeletal-muscle pain, fatigueness with the impossibility of maintain orthostatism, dispnea and dizziness. Clinical evaluation revealed normal blood pressure, IMC 34.7 kg/m^2 with pale skin. The paraclinic evaluation revealed undetectable values of ACTH <5 pg/ml with morning plasma cortisol concentrations of 3.14 microg/dl, respectively 7.93 microg/dl. Cortisol levels from the Synacthen test were 26.8 microg/dl, 34.6 microg/dl at 30 and 60 minutes respectively, but the normal values were correlated with the recent adrenal insufficiency. An incidental finding of a pituitary microadenoma was found on MRI. A diagnosis of tramadol-induced adrenal insufficiency was made. Other drugs containing glucocorticoids were excluded from her recent treatment. After three months under prednisone therapy 5 mg/day, the values of morning plasma cortisol 6.5 microg/dl and ACTH 11.16 pg/ml, with significant clinical improvement. Her prolactin levels raised to 52.6 ng/ml (RR 1.9–25 ng/ml), possible due to her secretant pituitary microadenoma.
Conclusion
This case raises awareness of the potential of opioids to influence adrenal status and is important that opiates should be added to the list of differential diagnosis in patients with newly diagnosed secondary adrenal insufficiency.

Keywords: opioids, Synacthen test, secondary adrenal insufficiency.
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P91

Intracerebral hemorrhage as a first sign of pheochromocytoma

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Pheochromocytomas and sympathetic paragangliomas are rare catecholamine-secreting tumors and represent very rare causes of intracerebral hemorrhage in young. Few cases of these neuroendocrine tumors which presented with intracerebral hemorrhage have been reported. A 32-year-old man presented to

our emergency department because of sudden onset of severe headache. He has a six months history of headache, palpitations and sweating. During examination he became somnolent and developed hemiplegia of the left side of the body. A computed tomographic scan of the brain showed a right temporoparietal hematoma. He was admitted to the Clinic for Neurosurgery and hematoma was evacuated. The patient was comatous, on assisted respiration and developed hypertensive crises. An examination for possible secondary causes of hypertension was undertaken. Plasma metanephrine value was elevated (414 pg/ml, reference values $<$90 pg/ml). Abdominal computed tomographic scans revealed a large mass (6 cm) in the right adrenal gland. After adequate control of the hypertension was achieved with an nonselective α and β adrenergic blockers, the tumor was excised. The histopathologic findings confirmed the diagnosis of pheochromocytoma. The genetic analysis demonstrated a duplication in exon 1 of VHL gene. We reported a rare, potentially fatal complication of pheochromocytoma, an intracerebral hemorrhage. This case and review of the similar rare cases in the literature illustrate the importance of early recognition of the characteristic symptoms of catecholamine excess in a young patient with hypertension.

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Severe pheochromocytoma crisis, Type B, resulting in Takotsubo-like cardiomyopathy and fulminant refractory cardiogenic shock, successfully treated with extracorporeal membrane oxygenation (ECMO) but with fatal neurological sequelae for the patient.

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Introduction
Catecholamine excess causes profound vasoconstriction, resulting in reduced intravascular volume. Pheochromocytoma crisis can be further complicated with acute stress (Takotsubo-like) cardiomyopathy, attributed to the toxic catecholamine effect on the myocardium, and cardiogenic shock leading to tissue ischemia.
Aim
To present a rare case of pheochromocytoma crisis, complicated with fulminant cardiogenic shock, which led to life-threatening end-organ damage.
Case report
A 34-year-old woman presented with a recent history of paroxysmal hypertension, palpitations and concomitant sweating. Echocardiogram and abdominal ultrasound had revealed a normal left ventricular ejection fraction (LVEF$>$55%) and a 7 cm mass in the right adrenal gland. Subsequently, she was admitted to the Endocrinology department, where hormonal workup showed elevated 24-h urine fractionated metanephrines and normetanephrines [18 266 μg/24 h (NR$<$800 μg/24 h) and 12 609 μg/24 h (NR$<$444 μg/24 h) respectively]. However, during the initial workup, the patient's condition deteriorated dramatically over a few hours, with no obvious physical, emotional or pharmacological triggering factor, following two episodes of hypertensive peaks (BP$\sim$200/120 mmHg) with symptoms of acute chest and abdominal pain, excessive weakness, sweating, pallor and wide fluctuations of blood pressure. Urgent electrocardiogram showed ST-segment depression in V4-lead and transthoracic echocardiography revealed a reduction of LVEF to $\sim$15% and a Takotsubo-pattern image of diffuse hypokinesia with apical ballooning. Phenoxybenzamine treatment was initiated immediately. Active haemorrhage or eruption of the adrenal tumour was excluded with emergency abdominal CT scan. The patient was transferred to the Cardiologic Intensive Care Unit, where her condition continued to deteriorate with abruptly elevated levels of cardiac enzymes and worsening tachycardia (160 bpm) non-responding to phenoxybenzamine and esmolol. Coronary artery angiography was normal. Despite attempts of cautious volume expansion the patient rapidly developed refractory cardiogenic shock, incipient multiple organ failure and hyperlactatemia (9 mmol/l) leading to intubation and initiation of central VA-ECMO support. Cardiac function was progressively restored and VA-ECMO was removed on day 12, with an LVEF$>$50%. Treatment with phenoxybenzamine was continued and right adrenalectomy was performed 18 days later. However, the patient's course had been complicated further with severe central nervous system damage, rhabdomyolysis and lower limb amputation due to thromboembolic events and hypoperfusion, with subsequent fatal hospital infections after a long-term ICU hospitalization.
Conclusion
Pheochromocytoma crisis can fulminantly develop into Takotsubo-like cardiomyopathy and refractory cardiogenic shock with fatal complications. In such perplexing cases, central VA-ECMO might be one of the few life-saving measures to be considered until myocardial function recovers allowing further management and surgical intervention.

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P93

Functionig adrenal incidentaloma false positive for 18F-FDG-PET/TAC

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An adrenal incidentaloma $>$4 cm of size is considered suspected of malignancy and therefore often sent to the adrenalectomy for pathological verification. In these cases, in recent studies the role of 18F-FDG-PET / TAC has been evaluated. We report a case of 67 years old man hospitalized for abdominal pain, fever and oliguria in obese patient with a history of diabetes mellitus 2, chronic renal failure, arterial hypertension and subjected to PTCA about 10 years earlier for anterior descending coronary stenosis. The abdominal ultrasound shows hepatic steatosis, many microstones of the gallbladder and an adrenal lesion of about 4 cm. Blood and uroculture detect a gram positive sepsis and laboratory tests show a cholestatic jaundice with moderate hyperamylasemia as well as renal failure and worsening glycemic control. After a few days of adequate therapy with a marked improvement in clinical conditions and laboratory tests, the patient undergoes, a cholangioMRI that detects, in addition to cholelithiasis, a solid right adrenal lesion of 4.8 cm, without adipose content and with non-homogeneous enhancement. The 18F-FDG PET/CT in the suspicion of a malignant lesion has been performed which showed a hypermetabolism of the right adrenal adrenal lesion (SUV max 12.8). There was non uptake in other lesions. The dosage of adrenal hormones showed a pre-clinical hypercortisolism ACTH-indipendent with normality of mineralocorticoid serum levels and urinary metanephrines. The patient was sent to laparoscopic cholecystectomy and right adrenalectomy. The morphological and immunophenotypic pathological analysis show a picture of a mixed type adrenal oncocytoma.
In conclusion:
1. It is confirmed that adrenal incidentalomas $>$4 cm may not be malignant.
2. Also the 18F-FDG-PET/TAC positivity is not always specific to malignant lesion.
3. The adrenal oncocytoma, very rare adrenal tumor usually benign and non-functioning, can be considered in these cases.

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Difficult Management of Autoimmune Polyglandular Syndrome Type 1

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Autoimmune Polyglandular Syndrome Type I (APS 1) is a rare monogenic disease, in which simultaneous or sequential dysfunctions of endocrine or nonendocrine glands appear. A 19-year-old woman was admitted for inappetence, nausea, vomiting, abdominal pain, chronic constipation, generalized paresthesia and vertigo. She was known with primary hypoparathyroidism (from the age of 5),

chronic autoimmune thyroiditis, mucocutaneous candidiasis, under treatment with calcitriol, calcium, magnesium and levothyroxine. The relevant clinical signs were periorbital, peribuccal and mucosae hyperpigmentation and in the areas exposed to pressure, but also hypotension and oligomenorrhoea. Laboratory assays revealed hepatocytolisis, hyponatremia (natrium: 118 nmol/l), hyperkalemia, hypoglycemia and hypocalcemia (ionic calcium: 4.05 mg/dl). Hormonal investigations indicated low cortisol value at 0800 h of 5.92 μg/dl, high ACTH level of 1092 pg/ml, decreased parathyroid hormone level of 2.5 pg/ml and normal thyroid stimulating hormone and free thyroxine values under levothyroxine. Follicle stimulating hormone (FSH) concentrations were high (23.4 μUI/ml), with low estradiol (<20 pg/ml), raising the suspicion of an ovarian insufficiency. The short Synacthen test revealed adrenal insufficiency. Taking into the consideration the association of the autoimmune diseases, the suspicion of APS1 was confirmed. An autoimmune hepatitis was excluded by specific negative antibodies. The endoscopy revealed chronic gastritis and the abdominal ecography indicated ovaries with follicular images. Large volumes of 0.9% saline were administrated and specific mineralocorticoid replacement was required. Hydrocortisone in bolus dose was adminstrated intravenous, and continued by oral therapy. After initiation of hydrocortisone treatment, a period of severe hypocalcemia followed, despite adequate intake of calcium and calcitriol. In contrast, under hydrocortisone substitution treatment, the menstrual cycle was adjusted, with normalization of estrogen and FSH levels at 2 months. In conclusion, we present a classic case of APS 1, but where hydrocortisone therapy for primary adrenal insufficiency has temporarily disturbed the calcium balance, but has normalized the ovarian function.

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Pitfalls in differential diagnosis of adrenal masses

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Introduction
Primary adrenal insufficiency (PAI) is a potentially life – threatening condition. About 75–80% of cases of PAI are caused by autoimmune destruction, while TB accounts for 7–20% of cases; however, adrenal tuberculosis is still the primary cause of PAI in developing countries. Adrenal tuberculosis is difficult to diagnose because symptoms are non-specific. Moreover, if the patient had no prior contact with TB patients, no past history of pulmonary TB and no active pulmonary lesions at presentation, the diagnosis is more difficult. The diagnosis is therefore often delayed and patients may first present with a life-threatening crisis.
Case report
An 63-year-old male patient was admitted in surgical department for important weight loss (30 kg in 12 months), weakness, nausea, fatigue and loss of appetite, mental confusion and dizziness. A chest and abdominal CT-scan with intravenous contrast revealed multiple mediastinal adenopathies and bilaterally enlarged adrenal glands with unomogenous nodular lesions (on the right – 16/13/22 mm, on the left – 50/38/47 mm) with diffuse calcifications and heterogeneous peripheral enhancement, highly suggestive for malignant tumors. He was directed to our clinic for specific investigations. At admission he was semiconscious and had low blood pressure – 90/60 mmHg and heart rate – 90/min. On physical examination slightly hyperpigmentation of the skin and buccal mucosa was observed. Blood results revealed hyponatremia, hyperpotassemia, *hypochloremia* and hypoglycemia. Serum cortisol level was <1 μg/dl and serum ACTH was >1250 pg/ml, confirming primary adrenal insufficiency and high dose intravenous hydrocortisone therapy was initiated rapidly. The patient general symptoms greatly improved under iv Hydrocortisone and he was redirected for surgical intervention, undergoing left suprarenalectomy. Histopathological examination revealed typical granulomatous inflammation with Langhans giant cells and caseous necrosis, the tissue PCR test confirming the presence of *Mycobacterium tuberculosis*. The patient was transferred to a tuberculosis hospital for specific treatment, a combination of four drugs was administered in addition to oral Hydrocortisone and Fludrocortisone. Over the next few weeks the patient's status markedly improved.
Conclusions
Computed tomography play vital role in the diagnosis of the PAI etiology, yet CT findings cannot always differentiate TB from other adrenal pathologies such as fungal infections, hemorrhage or malignancy. In our case, malignancy could not be excluded without first obtaining tissue for pathological examination. Adrenal TB is rare but an important disease entity that must be identified early, requiring prompt treatment with antituberculosis drugs and appropriate steroid therapy.

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From gastric sleeve to diagnosis of a rare familial multiple endocrine neoplasia type 1

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is an autosomal-dominant hereditary disorder characterized by the presence of two of the three main endocrine tumors that are parathyroid, pituitary adenomas and enteropancreatic tumors.
Case-report
We report a case of a 71-year-old obese patient with repeated unsuccessful attempts to weight loss who was admitted to the surgical department for the bariatric treatment of obesity (BMI = 48,22 kg/m^2); the preoperatory evaluation discovered hyperparathyroidism and an adrenal adenoma. Evaluated in the Iaşi Endocrinological Department, was diagnosticated also with non-functional pituitary macroadenoma and anterior pituitary insufficiency, two non-functional neuroendocrine pancreatic tumors and Recklinghausen neurofibromatosis. He underwent minim invasive partial parathyroidectomy due to high calcium level with local anesthesia, but with recurrence of hyperparathyroidism after 6 months. He initially refused pituitary or pancreatic surgery, now is reconsidering pituitary surgery due to high anesthesic risk for the next subtotal parathyroidectomy. The pancreatic tumors was nonsecreting and no evolutive signs during 2 years. Family investigation revealed son with primary hyperparathyroidism (operated) and prolactinoma (Cabergoline), one daughter with primary hyperparathyroidism (operated) and pituitary prolactinoma (Cabergoline) and one daughter with hyperprolactinemia. The grandchildren were clinical investigated (no endocrine tumors) and genetical tested.
Conclusions
We reported a rare case of familial syndrome of Multiple Endocrine Neoplasia type 1 and simultaneous occurrence of bilateral adrenal adenomas and Recklinghausen neurofibromatosis in a patient clinically diagnosed as having MEN type 1.
Keywords: Multiple endocrine neoplasia 1, primary hyperparathyroidism, prolactinoma, Recklinghausen neurofibromatosis.

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Primary adrenal lymphoma in an HIV patient: a rare case of bilateral adrenal tumors

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A 44-year old male patient with HIV-1 stage C2 presented with intermittent fever and weight loss (10 kg in 3 months). He was being treated with tenofovir/emtricitabine and atazanavir, and had a CD4 levels of 705/mm^3 and HIV viral load of 1400 copies/ml. Upon admission, the complete blood panel showed anaemia and thrombocytopenia (haemoglobin: 75 g/l, platelets: 98 G/l), normal white blood cell count, normal hepatic tests and renal function, normal electrolytes and an elevated CRP (85 mg/l) and erythrocyte sedimentation rate (990 mm). Abdominal CT-scan showed bilateral adrenal tumours, 10×9×15 cm on the right and 11×8×6 cm on the left, without invasion of adjacent structures. PET-CT scan showed intense hypermetabolism of the adrenal masses. Bone morrow biopsy and flow cytometry were negative for lympho-proliferative disease. Plasma fractionated free metanephrines were normal, excluding pheochromocytoma. The patient had no physical signs of Cushing disease and morning plasma cortisol was 291 nmol/l. An adrenal biopsy was performed which showed primary effusion lymphoma, solid variant. The patient received chemotherapy treatment (associated with high dose glucocorticoids) which led to clinical improvement

and shrinkage of the adrenal masses (4×4 cm on the right and 3×2 cm on the left) at 4 months follow-up. Nevertheless, PET hypermetamolism of the adrenals persisted and right adrenalectomy was decided in order to rule out persistent disease. At that time, the patient had primary adrenal insufficiency, with low plasma cortisol levels (18 nmol/l in the morning and 211 nmol/l 1-h after injection of ACTH 250 mg) and high morning ACTH (75 ng/l). Histology confirmed disease remission. Differential diagnosis of bilateral adrenal masses includes bilateral pheochromocytoma, adrenal metastasis, bilateral adrenal carcinoma, haemorrhage, infection, congenital adrenal hyperplasia etc. Primary adrenal lymphoma is a rare cause, but is associated with adrenal insufficiency in more than 50% of cases. This is a rare case of extracavitary primary effusion lymphoma, solid variant, often associated with HHV8 infection, which was also found in our patient.

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High Adrenocorticotropic Hormone before and after bilateral adrenal surgery

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Introduction
Paraneoplastic Cushing syndrome is a rare form of endogenous ACTH (adrenocorticotropic hormone) dependent hypercortisolism. In some cases no overt ACTH secretion tumor can be found, which is why steroidogenesis inhibitors, and bilateral adrenalectomy remain the main therapeutic options.
Material and method
This is a case report investigated in several centers by performing biochemical, hormonal and imagery tests.
Case report
A 52-year female, without medical personal history was admitted for marked asthenia, muscle weakness, polyuria and polydipsia. Clinical examination revealed central obesity (BMI of 30 kg/m^2), enlarged supra-clavicle fat pads, blood pressure of 150/80 mmHg, hyperpigmented skin, legs edema. Hormonal profile showed high levels of morning plasma cortisol (634 mg/dl, normal 5–25 mg/dL), with loss of circadian rhythm, very high CLU (free urinary cortisol), of 4728 mg/24 h (normal 50–190 mg/24 h), high ACTH level (619.9 ng/l, normal 7.2–63.3 ng/l), non-suppression at low dose DXM (dexamatasone) and 2 day of 8 mg DXM, high testosterone level (2.16 ng/ml, normal 0.2–0.75 ng/ml). Biochemical parameters indicated hyperglycemia and high HgA1c (glycated hemoglobin of 10.2%, normal 4.8–5.6%), hypercholesterolemia, low potassium (1.84 mmol/l, normal 3.5–5.1 mmol/l), and hypocalcemia. No morphological changes were found on pituitary MRI (magnetic resonance imaging) and pulmonary CT (computed tomography) scan. Abdominal CT scan showed bilateral hyperplasia. PET-CT scan (positron emission tomography) revealed an uncertainty mesenteric mass measuring less than 1 cm. Diagnosis of paraneoplastic Cushing syndrome was established. All neuroendocrine tumor markers were in the normal reference range. Potassium supplements, insulin and methyrapone therapy were started, followed by bilateral adrenalectomy. A month later obvious clinical and biochemical improvement was achieved under therapy with glucocorticoid and mineralocorticoid therapy. Because ACTH level is still high (of 1329 pg/ml) a careful follow-up is required. The primary site of neoplasia is still under investigation.
Conclusion
Diagnostic and treatment of paraneoplastic Cushing syndrome are essential for limiting the metabolic consequences and improvement quality of life. Long life follow-up is needed especially for variants without obvious tumor.

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Addison's disease due to bilateral adrenal hemorrhage as the first presentation of diffuse large B-cell lymphoma

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A 49-year-old previously healthy man suddenly felt severe and constant bilateral lumbar pain. Clinical examination was otherwise normal. Abdominal CT scan showed subacute hematomas in both adrenal glands (sized 10 cm right and 8 cm left). Basic laboratory tests were completely normal. Hormonal testing excluded pheochromocytoma and other hormonally active adrenal tumors. Adrenal insufficiency was confirmed by short Synacthen test and substitution therapy with hydrocortisone was introduced. Mineralocorticoid supplementation was not needed. Prolonged closure times and platelet dysfunction on aggregometry were also found. History for previous bleeding episodes in the patient and his family was negative. Tests for antiphospholipid syndrome were borderline positive. Repeated abdominal ultrasound (US) examinations showed a decrease in size of both adrenal hematomas, so the patient was discharged with hydrocortisone supplementation. Three weeks later, few days before the planned outpatient follow-up visit, patient sought medical help because of worsening bilateral lumbar pain and extreme weakness. Diagnosis of adrenal crisis was made, so he was admitted and treated with intravenous hydrocortisone and analgesics. Several follow-up US exams showed a gradual increase in size of both adrenal hematomas. Follow-up CT scan confirmed further hemorrhage in both adrenals, the diaphragm and the lower part of the left kidney. Angiographically, several microaneurysms were shown in the parenchyma of both kidneys, without active bleeding. Only on contrast-enhanced US solid formations in both adrenals and in left kidney were visible. Fine needle aspiration biopsy of the tumor in the right adrenal was not diagnostic, however, histological biopsy confirmed diffuse large B-cell lymphoma. 18F-FDG-PET-CT showed disseminated disease with the involvement of both adrenals, kidneys, small intestine and pelvis. The patient was transferred to oncology. Bilateral adrenal bleeding is most commonly caused by trauma, anticoagulation treatment, sepsis, surgery, antiphospholipid syndrome, bilateral pheochromocytoma or metastases. Of note, radiological picture of bilateral adrenal bleeding may be mimicked by lymphomas and bilateral metastases of malignant melanoma. When solid tissue is confirmed by imaging, definitive diagnosis could be made by biopsy, but only after exclusion of pheochromocytoma. Large, bilateral adrenal tumors may cause Addison's disease, which, if left unrecognized, may also endanger the patient.

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17- α hydroxylase deficiency in an adult female patient with hypertention and hypokalemia

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Introduction
17- α hydroxylase deficiency, an autosomal recessive disorder, is a rare cause of Congenital Adrenal Hyperplasia (CAH). The disease is usally diagnosed during infancy and childhood. We present here a rare case of an adult woman with 17-α hydroxylase deficiency diagnosed for first time in adulthood.
Presentation
A 49 year old woman, with no previous medical history came to the emergency department of our hospital unconscious with GSC 3-4/15. A CT head revealed a cerebral hemorrhage for which the patient had surgery and was transferred to the intensive care unit (ICU). In ICU she had persistent hypertension and severe hypokalemia not responding to treatment. From her history and the clinical examination revealed lack of any secondary sexual characteristics and the patient had never had menstrual cycle. Biochemical examination showed severe hypokalemia (K 2.7 mmol/l) , metabolic alcalosis (PH 7.496) and basal serum cortisol was very low (0.925 μg/dl). ACTH (406 pg/ml) and progesterone (24.24 ng/ml) were elevated and she had high FSH (143 mIU/ml) and LH (46.66 mIU/ml), low estrogen (5 pg/ml), low plasma rennin (3.7 pg/ml), 17-OH-Pg (0.6 ng/ml), and testosterone (0.025 ng/ml). An abdominal CT performed which showed hyperplasia of both adrenal glands, (6.5 cm in diameter) and she had a normal female karyotype (46XX). Based in the above findings the diagnosis of 17-α hydroxylase deficiency was made and treatment with dexamethasone 0.5 mg and spironolactone 100 mg twice a day was initiated which resulted in blood pressure control and correction of the hypokalemia. The patient had a sister who had intra-abdominal testes removed in childhood, ambigous external genitalia, a male karyotype (46XY) and normotensive. Hormonal evaluation showed a very low serum cortisol, 17-OH-Pg, estrogen, testosterone and plasma rennin while ACTH, FSH, LH, progesterone were increased.
Conclusions
17- α hydroxylase deficiency is a rare form of CAH which can be underdiagnosed. Presenting features may vary within affected members of the same family. Blood pressure measurements should be carried out in all females presenting with hypogonadism and if hypertension is present 17- α hydroxylase deficiency might be suspected.

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Li-Fraumeni syndrome and adrenal tumours: case report

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Introduction
Li-Fraumeni syndrome is a rare disorder that greatly increases the risk of developing several types of cancer, particularly in children and young adults. It is a hereditary disease with high penetrance autosomal dominant transmission that is due, in 70% of the cases, to germline mutations in the gene TP53. The most common cancers associated with this disorder are brain tumors, sarcomas, breast cancer and adrenocortical tumors.
Methods
We describe the case of a young female brought by her parents to our clinic after observing premature pubarche.
Results
We report the case of a 2-year-old female with pubarche since 18 months old. Her parents had not observed any other sign of androgenisation. At inspection we observed grade 3 pubarche with clitoral hypertrophy and no premature telarche. Blood test showed pre-puberal gonadotropins and 17-β-Estradiol; markedly elevated androgens: DHEA-S 3640 µg/dl (Normal Range 33–280), 17-OH-Progesterone >20 ng/ml, Testosterone 1.9 ng/ml ($N<0.8$ ng/ml for adult women) and cortisol 23 µg/dl (Normal range: 5–20). Suspecting an adrenal tumour we performed an MRI showing a mass of 4.5 cm in left adrenal. Adrenalectomy was performed less than one month later showing a lesion with capsule conservation, very low mitotic index and a minimum focus of vascular invasion. This lesion was considered as benign as it did not meet the criteria of a malignant lesion. A complete family history was made: on her maternal branch she had a cousin of 2 years old recently diagnosed of adrenal carcinoma. No other history of tumours on this side of the family. Two of her father aunts died of cancer under the age of 30 years old (breast cancer and brain tumour). Genetic study showed a mutation in c375G$>$A of TP53 gene in our patient confirming the diagnosis of Li Fraumeni Syndrome. Both parents are being studied and also his little cousin. After surgery all androgen levels normalized and no new lesions had been discovered in periodic abdomen ultrasounds.
Conclusions
Although Li Fraumeni syndrome is a rare disease we should consider it as a possible diagnosis in young patients with adrenal tumours. We should remember the association of this disorder and adrenal carcinoma and take it in consideration during follow up in patients with diagnosis of Li Fraumeni Syndrome.

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Addison's disease due to bilateral adrenal hemorrhage as the firstpresentation of diffuse large B-cell lymphoma

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A 49-year-old previously healthy man suddenly felt severe and constant bilateral lumbar pain. Clinical examination was otherwise normal. Abdominal CT scan showed subacute hematomas in both adrenal glands (sized 10 cm right and 8 cm left). Basic laboratory tests were completely normal. Hormonal testing excluded pheochromocytoma and other hormonally active adrenal tumors. Adrenal insufficiency was confirmed by short Synacthen test and substitution therapy with hydrocortisone was introduced. Mineralocorticoid supplementation was not needed. Prolonged closure times and platelet dysfunction on aggregometry were also found. History for previous bleeding episodes in the patient and his family was negative. Tests for antiphospholipid syndrome were borderline positive. Repeated abdominal ultrasound (US) examinations showed a decrease in size of both adrenal hematomas, so the patient was discharged with hydrocortisone supplementation. Three weeks later, few days before the planned outpatient follow-up visit, patient sought medical help because of worsening bilateral lumbar pain and extreme weakness. Diagnosis of adrenal crisis was made, so he was admitted and treated with intravenous hydrocortisone and analgesics. Several follow-up US exams showed a gradual increase in size of both adrenal hematomas. Follow-up CT scan confirmed further hemorrhage in both adrenals, the diaphragm and the lower part of the left kidney. Angiographically, several microaneurysms were shown in the parenchyma of both kidneys, without active bleeding. Only on contrast-enhanced US solid formations in both adrenals and in left kidney were visible. Fine needle aspiration biopsy of the tumor in the right adrenal was not diagnostic, however, histological biopsy confirmed diffuse large B-cell lymphoma. 18F-FDG-PET-CT showed disseminated disease with the involvement of both adrenals, kidneys, small intestine and pelvis. The patient was transferred to oncology. Bilateral adrenal bleeding is most commonly caused by trauma, anticoagulation treatment, sepsis, surgery, antiphospholipid syndrome, bilateral pheochromocytoma or metastases. Of note, radiological picture of bilateral adrenal bleeding may be mimicked by lymphomas and bilateral metastases of malignant melanoma. When solid tissue is confirmed by imaging, definitive diagnosis could be made by biopsy, but only after exclusion of pheochromocytoma. Large, bilateral adrenal tumors may cause Addison's disease, which, if left unrecognized, may also endanger the patient.

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P103

Paraganglioma of the prostate: a case report

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Introduction
Extra-adrenal paragangliomas are neoplasms arising from cells of neural crest origin anywhere along the distribution of the sympathoadrenal neuroendocrine system. Nearly 85% are intra-abdominal, 12% are intrathoracic, and 3% are cervical. 1 Some of the unusual sites for paragangliomas include the kidney, urethra, urinary bladder, prostate.
Case report
A 27-year old man presented with sever hypertensive crisis. He had a medical history of high blood pressure since the age of 15 years old. The patient had recurrent crises of three classic symptoms of pheochromocytoma: headache, swatting and heart palpitation in association with markedly elevated blood pressure (220/100 mmHg). These crises are consistent and sever after ejaculation, associated with tremors weakness and abdominal pain. On exam the patient was 175 cm tall and weighed 94 kg. He had no signs of neurofibromatose type1, MEN type 2 or Von Hippel-Lindau syndrome. Laboratory data showed elevated metanephrines in 24-h urine collection for three consecutive days (20.94 µmol/l >4 times the upper limit of normal). NSE level was high 54.1 ng/ml (12.5–25). MRI of the body showed normal size prostate with a nodule on the right side measuring 9 mm, T_2 hyperintense with microcalcification. Adrenal glands were normal and no other lesions were seen on the rest of the body. MIBG sintigraphy showed no uptake (physiologic uptake in the urinary tract). Prostatectomy was indicated after medical therapy preparation. Unfortunately surgery was refused by the patient.
Conclusion
Prostatic paragangliomas are very rare tumors, with no more than ten cases reported in the literature. Because of the nonspecific clinical symptoms, it is difficult to give a definite diagnosis preoperatively. Biochemical studies can confirm the diagnosis of pheochromocytoma. However topographic diagnosis remains a challenge in ectopic pheochromocytomas.

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P104

A new gene – TMEM127 – in familial pheochromocytoma/ paraganglioma syndromes

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Introduction
Pheochromocytomas are catecholamine-producing tumors originated from the chromaffin cells of the adrenal medulla. Although usually sporadic, this tumors could be associated with germline mutations in about 40% of cases. TMEM127 has recently been identified as a novel gene conferring increased susceptibility to pheochromocytoma.

Case report
A 42-year-old woman was referred to our Hospital to perform a right adrenalectomy for pheochromocytoma. Months before she had hemoptysis, chest pain and arterial hypertension (180/120 mmHg) and performed a chest computed tomography that revealed a 6.5 cm right adrenal nodule with a density similar to liver parenchyma. During hospitalization, she presented several hypertensive peaks and performed an iodine-123MIBG Whole Body Scan that revealed increased uptake in the right adrenal gland. Urinary metanephrines and vanilmandelic acid were normal. She underwent phenoxybenzamine therapy and was submitted to right adrenalectomy by laparotomy. The histological exam confirmed the presence of a pheochromocytoma with probable aggressive biological behavior, proliferation index (Ki67) of 5% and preservation of the adrenal cortex. After the surgery, she presented normalization of blood pressure, normal values of urinary metanephrines and vanilmandelic acid and a slight elevation of chromogranin A, norepinephrine and 5-hydroxyindoleacetic acid. During the biochemical and imaging follow-up, the patient showed no signs of recurrence or new extra-adrenal foci and remains in regular surveillance without evidence of disease 7 years after surgery. A gene panel analysis was performed (SDHAF2,SDHB,SDHC,SDHD,VHL,MAX,TMEM127) and the c.202delG mutation in TMEM127 gene was found. A molecular study was carried out on first-degree relatives and two asymptomatic carriers (father and sister) were identified.
Discussion and conclusion
An increasing number of genes have been associated with familial pheochromocytomas/paragangliomas and are associated with different manifestations/risk of malignancy. Pheochromocytoma associated with this mutation is unilateral in 70% of cases and may be associated with the risk of extra-adrenal locations. We report the clinical case of a patient with familial pheochromocytoma with identified mutation in TMEM127 gene, present in heterozygosity. To the best of our knowledge, this is the first mutation in this gene described in the Portuguese population. The present case identifies an adrenal lesion with typical manifestations, with a histology suggestive of aggressive behavior, without manifestations of disease to date in the other two mutation carriers. These data emphasize the need for molecular study of a large panel of genes in patients with apparently sporadic pheochromocytoma.

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P105

Bilateral adrenal mass revealing a pheochromocytoma and an adrenocortical adenoma in a young women: a case report

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A 44-year-old women without personal or familial pathological history, presented 8 months before her admission a paroxystic symptomatology made of palpitations, headache and profus sweat associated with major abdominal pain, evolving in a context of alteration of the general state. Clinical examination objectified high blood pressure and tachycardia. Laboratory testing confirmed the diagnosis of pheochromocytoma. A computed tomography of the abdomen revealed a bilateral adrenal mass. The patient was treated with blood pressure treatment, specifically nicardipine and beta blockers, and surgical excision of the masses. Anatomopathological study objectived a right pheochromocytoma and left adrenocorticaladenoma. This case displays an atypical clinical presentation of bilateral adrenal masses.

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P106

Cushing's syndrome in a patient with systemic lupus erythematosus

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Introduction
Systemic lupus erythematosus is a systemic autoimmune disease, which often necessitates the administration of corticosteroids for its treatment. Cushing's syndrome is a disorder characterized by the endogenous hypersecretion of cortisol.
Aim
The aim was to describe the case of a patient who had systemic lupus erythematosus, was on therapy with corticosteroids and developed Cushing's syndrome.
Case description
A patient, female, aged 34, had systemic lupus erythematosus and was on therapy with corticosteroids. While on therapy with corticosteroids she developed depression, extreme fatigue, amenorrhea, face plethora and a buffalo's hump. Subsequently, she presented with a spontaneous fracture of the pubic rami, which she suffered while walking. The fracture was managed conservatively. Thereafter, the patient suffered a fracture of the left 5th metatarsal bone. A year later, she suffered a spontaneous rib fracture. Bone densitometry revealed a T-score of -2.5 in the lumbar spine. Corticosteroids were discontinued. Further laboratory evaluation revealed urinary cortisol 235 μg/24 h (normal range 3.5–45 μg/24 h), morning cortisol 17.7 μg/dl and ACTH 1.2 pg/ml (normal range 7.2–64 pg/ml). An MRI of the abdomen revealed the presence of an adenoma measuring 3×2 cm in her left adrenal. The adenoma was surgically excised. A month later laboratory evaluation revealed low morning cortisol and hydrocortisone was administered. Menses recommenced and face plethora was no more evident. Systemic lupus erythematosus was managed by azathioprine. A year later bone densitometry revealed a T-score of -2.2 in the lumbar spine.
Conclusions
In conclusion, the case of a patient with systemic lupus erythematosus is presented who developed Cushing's syndrome. Cushing's syndrome was due to the presence of an adrenal adenoma. In the case presented Cushing's syndrome manifested with amenorrhea, fatigue and spontaneous osteoporotic fractures in a very young patient. The diagnosis was masked by the therapeutic administration of corticosteroids. In a young patient spontaneous fractures should prompt a diagnostic evaluation for endocrine causes of osteoporosis.

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Clinical case reports - Thyroid/Others

P107

Searching for the cause of high HCG in a man

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Beta-human chorionic gonadotropin (β-hCG) is normally produced by syncytiotrophoblasts of the placenta and may also be secreted by germ cell neoplasms. An increase of serum hCG concentration in a male patient often suggests malignant neoplasms with a trophoblastic element. Common examples include classic seminoma with syncytiotrophoblast-like giant cells, combined germ cell tumour, and choriocarcinoma. Non-gestational choriocarcinomas typically arise from gonadal organs but they may originate in extragenital sites such as the mediastinum, retroperitoneum, pineal gland, liver, gallbladder, and urinary tract. Ectopic secretion of β-hCG is associated with a poorer prognosis. We present a 50 year old man who was referred to endocrine clinic with painful gynaecomastia of 3 months duration. He was waiting hip replacement. He had history of a lump in his left breast 9 years ago. He had USS and FNA. He was treated with some tablets for a month and discharged from breast clinic. He had no other past medical history. He worked as a physical trainer to metropolitan police. He did not smoke or drink and was on no medication. He had never used recreational drugs. His BMI was 26 kg/m^2. Examination and USS confirmed bilateral gynaecomastia. USS of the testes was normal with a small hydrocele on the left side. His blood tests showed FSH of <0.1 (1–10 IU/l), LH <0.1 (2–9 IU/l), testosterone 36.2 nmol/l (6.68–25.70), oestradiol 354 pmol/l (99–192), SHBG 44 noml/l (20.6–76.7) and his HCG was 250 IU/L (0–2). CT thorax, abdomen and pelvis was reported to be normal. His whole body bone scan was normal. His Repeat HCG in 6 weeks was 1265 and subsequently in 3 months increased to 3756. He underwent NM Whole body FDG PET CT which raised suspicion of an aggressive lesion in the anterior mediastinum with metastatic deposits in the lung. Mediastinal biopsy showed no unequivocal evidence of malignancy and a panel of immunohistochemical stains was not contributory. He had elective left anterior mediastinotomy +-VATS. Anterior mediastinal mass biopsies confirmed choriocarcinoma.

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P108

Syndrome carney-stratakis, new mutation report: SDH B: D138Y (c.412>T)

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Introduction
The Carney-Stratakis syndrome (CSS) is an inherited condition caused by germline mutations in succinate dehydrogenase (SDH) subunits B, C or D that predispose to gastric stromal tumors (GIST) and multicentric paraganglionas (PGL). SDH acts as a tumor suppressor gene, and enzyme activity reduction is known to be oncogenic. Since 2002 there has been some scarce reports. We present a new case of CSS associated with a germline unknown significance mutation in exon 4 of the gene that encodes SDH complex subunit B.
Case presentation
In July of 2016, a 52 year old women was referred to study a 94×97 mm abdominal mass in hepatic hilum. She had a past medical history of multiple PGL. In 1995 at 31 years old, underwent a retroperitoneal hyperfunctional PGL resection and since then she had performed subsequent clinical controls with annual catecholamines/metanephrines and bi-annual cervical and thoraco-abdominal examinations. Gene analysis revealed a germline mutation (c.412> T) in SDHB. The familial gene analysis showed that her mother and son were unaffected carriers. At the 2012 control CT, a 7 × 6 mm nodular lesion was detected in the left carotid bifurcation suggestive of PGL. Surgical therapy was discarded due the small size of the tumor. Neither increase nor new cervical PGL were observed during close follow-up and catecholamines and metanephrins remained negative. First, the patient was admitted to another hospital in context of abdominal and dorsal pain and an enhanced CT evidenced a pseudonodular hepatic image 94 × 77 mm in size with intrahepatic and extrahepatic portal thrombosis up to the head of the pancreas. The patient was referred to our hospital and a diagnostic study was started. NMR revealed an infiltranting intra-abdominal mass, with intraportal dissemination and a negative MIBG; Chromogranin A was elevated and neurospecific enolase and other tumor markers were Negative; Eco-endoscopy transgastric-PAAF was diagnostic of GIST (Positive to Vimentin, CD34, CD117, WT1; Ki-67 of 60%; Absence of mutations of the KIT gene). Final diagnosis and treatment: GIST T3N1M1 Stage IV. A 6 months partial response was observed with Imantinib, but it had to be suspended at 8th month because of morphometabolic worsening. Sunitinib was introduced and discontinued at second month of therapy for upper gastrointestional bleeding and liver function deterioration. Then palliative treatment with corticosteroids was started with clinical improvement and radiotherapy localized to hepatic hilium showed partial response; so it is decided to initiate Regorafenib.

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P109

Challenges in the diagnosis and treatment of GEP NEN: a case report

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Introduction
The GEP NEN (gastroentero-pancreatic neuroendocrine neoplasms) are 70% of all neuroendocrine tumors, but are rare in general population – constituting only 2% of the gastrointestinal tract neoplasms. Carcinoid stands for 50% of GEP NEN, most often located in the appendix and/or ileum. Although the detection of NEN is rising, their prevalence is still likely underestimated. The clinical presentation is not characteristic at the early stages of the disease, it varies among patients, what may make the diagnosis difficult to establish. We present a case of a man with certain clinical characteristics of carcinoid. Specific points suggesting a GEP NEN and critical to the clinical practice are discussed.
Case report
A 65-year-old man with the previous history of hypertension, atrial fibrillation with tricuspid valve insufficiency, DM2 and a few small liver haemangiomas discovered in 2013, was referred to internal diseases department in Wroclaw in 2016. He actually complained of poor hypertension controll, sporadic diarhoea, not significant weight loss. Performed abdominal CT scans revealed multiple large liver lesions both with enlarged regional lymph nodes of suspected metastastatic origin. Other CT scans and endoscopic investigations found no primary tumor, except few gastric erosions, diverticulosis coli and benign rectal polyp. On account of the patient's slight recurrent flushes reported in a deepened interview and echocardiography revealing endocardial fibrosis with advanced degeneration of the tricuspid valve (regurgitation), the GEP NEN was suspected. Performed Tectrotide somatostatin receptor scintigraphy SPECT CT Tc99m was negative, CgA concentration was 425ng/ml and finally liver biopsy material with immunohistochemistry confirmed metastatic NEN G1. Next PET CT 18F-FDG scan revealed metabolically active lesion in the ileum, which was confirmed in Galium 68 PET(neoplasm with high expression of somatostatin receptors of the smal intestine from dissemination to mesenteric lymph nodes and liver). Due to advanced heart failure the primary tumor of the ileum was not treated surgically. The patient receives chronically Sandostain LAR, he underwent also 177Lu Dotatate therapy in Oncology Center, Gliwice. The size and number of the liver lesions are under controll.
Conclusion
Carcinoid diagnosis needs various imaging techniques and histopathological evaluation, but clinically accuracy is of greatest importance. Incidental occurrence of liver lesions suggests the need for the GEP NEN screening, at least evaluation of CgA and/or CT control, especially in the case of accompanying the right heart valve abnormalities. Early treatment is crucial to avoid dissemination of the disease and life-threatening complications.

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Endocrine tumours and neoplasia

P110

Ectopic adrenocorticotropic hormone syndrome: clinical features, diagnosis, treatment and long-term observation. Impact of bronchial carcinoid tumors

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Objective
Ectopic adrenocorticotropic hormone (ACTH-ectopic) syndrome (EAS) is a rare cause of ACTH-dependent endogenous hypercortisolism. The objective of this study was to analyze the clinical, biochemical, and radiological features, management, and treatment outcome of patients with EAS.
Methods
It was a retrospective case-record study of 47 patients with EAS. Clinical, biochemical, and radiological features and response to therapy and survival rate were measured.
Results
The median follow-up was 7 yrs. (range, 1–13 yrs.). None of the dynamic tests achieved 100% accuracy. Imaging correctly identified the lesion at first investigation in 80.9% of cases. Bronchial carcinoid tumors were the most common cause of EAS ($n=27$; 57.5%), followed by other neuroendocrine tumors ($n=11$, 23.4%). In 19.1% (9) of patients, the source of EAS was never found. Octreotide scintigraphy and whole-body venous sampling were of limited diagnostic value. Surgical attempt at curative resection was successful in 81% (38 out of 47) of all patients; 9 (19.1%) responded generally well to bilateral adrenalectomy by vital indication. Tumor histology and the presence of distant metastases were the main predictors of overall survival ($P<0.05$).
Conclusions
Bronchial carcinoid tumors is the main cause of ACTH-ectopic syndrome. No single test was capable of finding the source of EAS correctly. Despite a variety of tests and imaging studies for the correct diagnosis of the EAS, up to 19% of cases present as occult EAS syndrome. These cases require a prolonged follow-up, review, and repetition of diagnostic tests and scans, but, in severe cases, bilateral adrenalectomy is performed.

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P111

Effect of ^{177}Lu-dotatate on severe, life-threatening, and refractory hypoglycemia associated with malignant insulinoma

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Malignant insulinoma is an extremely uncommon tumor (5–10% of insulinomas). It is accompanied by severe hypoglycemia and a short life expectancy (survival at 10 years <10%). Its clinical management is complex and constitutes a real therapeutic challenge. So far, the experience of radionuclide treatment in these tumors is scarce. We report the case of a 51-year-old woman diagnosed with pancreatic neuroendocrine tumor (pNET) in January 2013. Pre-surgical imaging study by abdominal CT scan showed a hypodense image in the tail of the pancreas with multiple liver metastases and large (up to 14 cm) ovarian masses. She underwent surgery on 09/01/2013 by exploratory laparotomy performing bilateral adnexectomy with pathological result of large cell neuroendocrine carcinoma (Ki-67 60%). The post-surgical [111In] DTPA-octreotide scintigraphy (Octreoscan) revealed hypercaptant lesions in the pancreatic tail, beginning treatment with lanreotide autogel 120 mg/28 days and sunitinib 37.5 mg/day, achieving a stabilization of the pancreatic and hepatic lesions. After tumor progression, she received six cycles of chemotherapy (cisplatin-etoposide) with partial response (50% size reduction) of the pancreatic lesion and stabilization of the liver metastases. After the 3rd cycle, she began to have severe and repeated hypoglycemic episodes with neuroglycopenic symptoms and frequent loss of consciousness even with seizures. Despite treatment with everolimus (10 mg/day for 3 months) and later with steroids (methylprednisolone, 32 mg/day), diazoxide (150 mg/day) and octreotide long-acting release (LAR) (30 mg/2 wk) the patient continued with frequent severe hypoglycemia (blood glucose 20 mg/dl, serum insulin 132 mU/ml and serum peptide C 18.7 ng/ml). On 21/07/2017, a first dose (177 mCi) of ^{177}Lu-DOTATATE was administered. After 10 days, the patient reported a clear clinical improvement, disappearing symptoms of hypoglycemia, showing an adequate control of capillary blood glucose throughout the day. In her last clinical visit in January 2018, after three doses of ^{177}Lu-DOTATATE (total dose 577 mCi), the patient continued without symptoms of hypoglycemia without the need to take diazoxide. The only treatment at this time was glucocorticoid replacement therapy and SSA (octreotide long-acting release LAR, 30 mg/2 wk). With this medication analytical study showed a blood glucose level of 115 mg/dl with normal serum insulin (20.3 mU/ml) and C-peptide (5 ng/ml) levels. In conclusion, ^{177}Lu-DOTATATE effectively and early controls severe hypoglycemia associated with malignant insulinoma. Therefore, we suggest its use in early stages of symptomatic disease not controlled with medication.

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P112

Morphological changes of the adrenal glands with hypertension with a crisis current

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Assess the morphology of focal lesions of the adrenal glands after adrenalectomy, compare the results with the nature of the course of hypertension, the level of blood pressure, age, sex of patients.
Materials and methods
Forty-four medical maps of patients operated on for focal formations of the adrenal glands were analyzed. The clinical symptoms, the hormonal activity of adrenal gland tumors - the level of cortisol, aldosterone, potassium, sodium, renin activity of blood, metabolites of catecholamines were analyzed.
Results
Thirty-two patients (72.7%) had adrenal hypertension, 12 (27.3%) had no hypertension. In the group of patients with adrenal hypertension, women predominated - 26 (81.3%) and 6 men (18.7%), mostly of working age (50.5 $\pm$ 5.2 years). The reason for visualization of the adrenal glands in patients with hypertension was its crisis course, resistance to antihypertensive drugs. The reason for visualization of the adrenal glands in patients without hypertension was a diverse somatic pathology. All patients underwent unilateral adrenalectomy. In 87.5% of patients with adrenal hypertension, of which women predominated (78.6%) older (53.1 $\pm$ 3.2 years) than men (44.4 $\pm$ 4.7 years; $P<0$, 05), hormonally active adrenal tumors were diagnosed: pheochromocytoma in 50%, adrenocorticosteroma and aldosteroma in 35.7% and 14.3% of cases, respectively. The remaining 12.5% had hormonally inactive adrenal formations, hence there was essential hypertension. These patients were significantly older than patients who had hormonally active adrenal formations: 65.1 $\pm$ 2.4 and 51.5 $\pm$ 5.1 years ($P<0.05$), and the blood pressure level was lower: 160/100 $\pm$ 10/15 against 196.4/100 $\pm$ 20/10 mm Hg. ($P<0.05$). The results of a histological study of adrenal removed adrenal glands in patients without hypertension revealed "dumb" tumors of chromaffin tissue in 16.7% of cases. The obtained results testify to the necessity of searching for secondary hypertension of adrenal genesis in all patients with hypertension characterized by a crisis current.
Conclusions
1. In most cases (87.5%), the course of hypertension in patients operated on for focal formation of the adrenal gland is due to a hormone-active tumor.
2. Hormonal-active tumors of the adrenal glands in patients with a crisis course of arterial hypertension are represented in 50% of cases by pheochromocytoma, in 35.7% by adrenocorticosteroma, in 14.3% by aldosterome.
3. The creeping flow of arterial hypertension of the adrenal genesis is more often diagnosed in middle-aged women, accompanied by higher figures of arterial pressure.

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P113

Atypical manifestation of adrenocortical carcinoma – case series

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Adrenocortical carcinoma (ACC) is a rare malignancy. Authors present three cases of even less commonly encountered manifestation of ACC. Case 1: A 39-year-old male, with decompensated hypertension, was admitted to Department of Endocrinology due to a large tumor of the left adrenal gland (65 mm) revealed in the CT of the abdomen. Non-contrast attenuation was 35HU. After performing MRI with chemical shift, tumor was classified as non-adenoma as there was no significant loss of signal in out-of-phase sequence. Excess of cortisol and aldosterone was excluded, but urine metoxycatecholamines remained in upper limit of the norm. Scintigraphy with iodine-123-meta-iodobenzylguanidine and somatostatin receptor revealed increased uptake of radiotracers in left adrenal gland. The patient was diagnosed with pheochromocytoma and after two weeks of alfa-blocker intake he underwent surgery. The pathology report revealed ACC. Case 2: A 54-year-old woman, with hypertension and incidentalomas of both adrenal glands diagnosed in 2011 was referred to Department of Endocrinology in 2017. In 2011, due to anaphylactic reaction to iodine in medical history, only single-phase CT was performed which revealed a tumor of left adrenal gland (25 mm) of density 16 HU. Hormonal activity was excluded and the patient was diagnosed with lipid poor adenoma. One year later, CT was repeated and there was no tumor growth so the follow-up was ended. In 2017 the tumor was classified as non-adenoma based on MRI with chemical shift (very low lipid content) and the possible autonomous cortisol secretion was revealed during hormonal work-up. There was non-specific accumulation in left adrenal gland in somatostatin receptor scintigraphy and the patient underwent adrenalectomy. The pathology report, revealed myelolipoma together with ACC infiltrating the fat tissue. Case 3. A 50-year-old male reported to the emergency room due to severe hypertension, hypokalaemia and tumor in right adrenal gland (32 mm). In CT attenuation before contrast was 29HU and absolute contrast enhancement washout was 57%, so lipid poor adenoma was diagnosed. Hormonal evaluation excluded hypercortisolemia, aldosterone concentration was 123 pg/ml, PRA 0,12 ng/ml/h, therefore ARR was high $=102$. The primary hyperaldosteronism was confirmed in saline infusion test and lateralization in adrenal venous sampling. Patient underwent laparoscopic adrenalectomy. The pathology report revealed ACC.
Conclusion
Though ACC is rare, it should be taken into consideration in every case of non-adenoma phenotype in imaging examinations. Thorough meticulous evaluation in imaging is necessary to identify all cases of ACC, regardless of hormonal activity.

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P114

Are there any clinical predictor for malignancy in malignant pheochromocytoma?

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Introduction
Malignant pheochromocytoma (MPheo) is diagnosed by the presence of invasion of adjacent structures or distant metastasis. Predictive factors of malignancy for pheochromocytoma (Pheo) are not well known.
Material and methods
We retrospectively analyzed clinical, biochemical, radiological characteristics as predictors for malignancy in patients with Pheo in two Spanish tertiary hospitals during the past 35 years. We also evaluated time of recurrence, most frequent locations of metastatic lesions, and surgical and other therapeutic modalities.
Results
We reviewed 80 patients diagnosed with Pheo (8 MPheo, 10%). Metastatic disease/invasion of adjacent structures was present in 4/8 at the time of diagnosis, and become evident in 4/8 after surgical removal of the primary tumor, within 7 years (range 1–8). Age at diagnosis was similar in both groups (MPheo 52.1yrs; range 15–73 vs Pheo 51.5yrs, range 13–76; ($P=0.481$)). Males comprised 62.5% versus 40.8% of the MPheo and Pheo group, respectively. ($P=0.216$). Prevalence of hypertension was similar in both groups [MPheo, 3/8, 3/8 (37.5%) and non-MPheo 32/72 (44.4%); $P=0.109$]. All 8 MPheo patients had elevated catecholamines (urinary and/or plasma) with an average of 5.6 times the reference value. MIBG imaging was performed in 4/8 patients, and all of them had positive scans. MPheo was unilateral in 7/8 patients; the patient with bilateral MPheo was diagnosed of MEN2a. Tumor size was significantly higher in MPheo than in non-MPheo patients (10.1 vs 5.7 cm, $P=0.038$). Metastatic lesions were found in the liver ($n=4$), bone ($n=3$), vascular ($n=3$), and distant lymph node ($n=2$). Resection of the primary mass was performed in 2 out of 4 patients with initial metastatic disease. 2/8 MPheo patients underwent surgery of metastatic lesions. Non-surgical treatment was also implemented in 6/8 (75%), 5/6 received high-dose MIBG and 1/6 chemotherapy (vincristine, dacarbazine and cyclophosphamide). Evaluation of the best overall response according to the RECIST1.1 Criteria was conducted in 6 out of 8 MPheo. Complete response was achieved in 2/6 patients (one treated with chemotherapy and another with high-dose MIBG; cumulative dose of 600mCi). Partial response was found in 1/6, and tumor progression was assessed in 3/6. Mean follow-up was 6 years.
Conclusion
No association was found regarding age or sex on the development of MPheo. The only clinical difference between MPheo and non-MPheo was the greater tumor size at diagnosis in the former. Due to the absence of clear predictors for malignancy in Pheo, long-term follow-up after surgery is mandatory in these patients.

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P115

New cancer drug targets identified in adrenocortical carcinoma through gene expression profiling

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Adrenocortical carcinomas (ACC) are associated with heterogeneous prognosis and limited treatment options for advanced stages. Until now no efficient targeted therapies have been identified. This study aims to identify possible new molecular drug targets for a future personalized therapeutic approach. We isolated good quality RNA from 40 formalin-fixed paraffin-embedded tumor samples (33 from primary surgery, 5 from local recurrences and 2 from distant metastasis) of ACC patients (26F&14M, median age 46 yrs). Gene expression of 84 known cancer drug targets was evaluated by RT^2 Profiler PCR Array (Qiagen). Fold change (FC) was calculated with the 2^(-DDCT) formula using 5 housekeeper genes and 5 normal adrenal glands (NAG) as reference (overexpression by FC$>$2.0). The expression of selected candidates was validated at the protein level by immunohistochemistry in the same series. The 6 most frequently overexpressed genes were *TOP2A* (100% of cases, median FC$=$16.5), *IGF2* (95%, FC$=$52.9), *CDK1* (80%, FC$=$6.7), *CDK4* (62%, FC$=$2.9), *PLK4* (60%, FC$=$2.8) and *PLK1* (52%, FC$=$2.3). Several members of AURK and HDAC gene families (e.g. the) were also overexpressed. mRNA expression of *AURKA, CDC25A, CDK1, CDK2, HDCA2* and *TOP2A* positively correlated with ki67 proliferation index (all $P<0.05$). CDK1, CDK4, PLK1 and TOP2A were selected as candidates for validation by immunohistochemistry. Interestingly, nuclear staining of CDK1, CDK4 and PLK1 significantly correlated with mRNA expression ($R=0.64$, $R=0.52$ and $R=0.55$, respectively, all $P<0.005$). In conclusion, we identified by gene expression profiling interesting targetable genes that might serve as basis for personalized therapy in advanced ACC. The expression of these candidates might be investigated by immunohistochemistry in the clinical practice. For instance, *CDK4* is overexpressed in several cancers and can be targeted by CDK/CDK6 inhibitors (e.g. palbociclib) that are currently tested in numerous clinical trials on solid tumors. Validation and functional studies on ACC cell lines are ongoing to confirm present results.

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P116

Outcome of adjuvant mitotane therapy in patients with adrenocortical carcinoma: the experience of San Luigi Gonzaga Hospital

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Background and objectives
The role of adjuvant mitotane therapy after radical surgery for adrenocortical carcinoma (ACC) is still debated. The aim of our study is to assess the effects of adjuvant mitotane on recurrence free survival (RFS) and overall survival (OS) in non-metastatic ACC patients and to evaluate prognostic factors in adjuvant setting.
Methods
Retrospective data were collected from 152 patients affected by ACC (stage I-III) referred to our center from 1988 to 2015. One hundred patients underwent adjuvant mitotane therapy (mitotane group), while 52 patients did not receive any treatment after surgery (control group). The following potential prognostic factors were investigated with univariate and multivariate analysis: age at diagnosis, endocrine activity of the tumor, ENSAT tumor stage, R status, Weiss score, mitotic count, Ki-67, plasma mitotane levels.
Results
Although the patients on mitotane had a worse prognostic profile (higher Weiss score, mitotic count and Ki-67), we observed a significant increase in RFS of the mitotane group (median 37 [4–199] vs 21 months [4–180], HR 2.79 [1.58–4.91], $P<0.001$), while OS was not significantly different between the two groups (median 58 [8–199] vs 50 months [4–231], HR 1.22 [0.61–2.42]). In multivariate analysis hormonal secretion, Weiss score, mitotic count and Ki-67 were negative prognostic factors for RFS. The same factors with tumor stage were associated with a shorter OS.
Conclusions
Adjuvant mitotane therapy was associated with prolonged RFS in ACC patients. An effect on OS was not apparent but a longer follow-up is likely needed to evaluate any treatment-related difference.

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P117

Adrenocortical carcinoma – characteristics and outcome of patients treated at Helsinki University Hospital during the last 15 years

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Background
Adrenal cortical carcinoma (ACC) is a rare malignancy known to be highly aggressive, with few specific treatment options. The objective was to evaluate clinicopathological features and outcome in patients treated at Helsinki University Hospital
Methods and patients
We included all patients diagnosed with adrenocortical carcinoma (Weiss score $\geq$4) at Helsinki University Hospital during the years 2002 through 2017. Patients were identified from our electronic patient records using ICD-10 codes C74.0 and 74.9 and from the Pathology register. Data on presentation, surgical and medical treatments were retrieved from patient records. Radiologic and histopathological characteristics were re-evaluated.
Results
Forty-two patients were diagnosed and treated for ACC, five of which were children. Of the adult patients, 23 (62%) were women, mean age at diagnosis was 56 years (18–84). Median follow-up was 41 (1–199) months. Twenty-seven (75%) of the tumours were found incidentally. Abdominal pain was the most common symptom, occurring in 11/36 (31%) of the patients, 6/36 (17%) presented with hirsutism, 5/36 (14%) had bruises, and 2/23 (9%) menstrual disturbances. Fifty-four percent (19/35) had biochemically verified hypercortisolism, 19% (5/27) hyperaldosteronism and hyperandrogenism was confirmed in all the 11 females (48%) that were investigated for hyperandrogenism. According to ENSAT staging, 6/36 (17%) had stage I, 13/36 (37%) stage II, 8/36 (22%) stage III and 9/36 (25%) stage IV disease. Mean tumour size was 95 mm (20–196 mm) and, in 67% (24/36) the origin was the left adrenal. Mean Hounsfield units were 33 HU (21–45), mean Ki67 17% (1–40%), mean Weiss score 7.1 (4–9) and Helsinki score 24 (4–48). Thirty-three (89%) patients underwent primary surgery, metastases were resected in 4. Thirty (81%) received adjuvant mitotane therapy, therapeutic concentrations were reached in 18 (60%) in a mean of 334 days (78–1055), with a mean cumulative dose of 1030 g (168.5–1847.5). Treatment was discontinued in 9 (30%) patients because of adverse effects. Further oncological treatments were given to 35% (13/37). The 5-year survival rate was 67%.
Conclusion
To date, ACC often presents as an incidental finding. In contrast to benign incidentalomas, ACC is always characterized by a high HU ($>$ 20) on non-contrast CT. Of the patients, 31% presented with abdominal pain and 54% had biochemically verified hypercortisolism. In this cohort, 83% had at least stage II disease and the 5-yr survival rate of 67% was better than in most previous reports.

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P118

Comparative study between familial and sporadic pheochromocytoma

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Introduction
Pheochromocytomas (Pheo) may appear sporadically (SPheo) or as an autosomal dominant inherited disease, named as familial PHEOs (FPheo). The latter are present in younger patients, and usually with multiple tumors, but may occur in patients with apparently simple sporadic tumors with no other syndromic features.
Material and methods
Clinical data of all consecutive patients underwent surgery for Pheo over 35 years in two tertiary referral centers were collected. We compared clinical features, diagnosis, methods, type of surgery, complications and tumor behaviour between SPheo and FPheo patients.
Results
We reviewed 76 patients who underwent surgical resection of Pheo. Fourteen patients (18.4%; 7F) had FPheo and 62 patients (81.6%; 37F) had SPheo. The distribution of FPheo patients was as follows: MEN2A ($n=6$), NF-1 ($n=5$), VHL ($n=2$), and MEN2B ($n=1$). Age at diagnosis was significantly lower in FPheo than in SPheo patients (42.1$\pm$17.2 vs 53.6$\pm$14.5 yr; $P=0.014$). Persistent hypertension was more prevalent in SPheo than in FPheo patients (21.4% vs 51.6%; $P=0.041$). No differences were found in relation of the presence of Pheo classic triad (headaches, palpitations, and sweating) between both groups. Multiple Pheo were significantly more common in FPheo than in SPheo patients (35.7% vs 3.2%; $P=0.001$). We did not found significant differences in the percentage of patients with elevation of plasma and/or urinary catecholamine levels (81.8% in FPheo vs 72.5% in SPheo; NS). All SPheo were adrenal tumors whereas one FPheo was adrenal and abdominal ($P=0.034$). The tumor size was significantly lower in FPheo than in SPheo (4.0$\pm$2.0 cm vs 5.5$\pm$2.4 cm; $P=0.047$). There were no complications in FPheo patients compared to 16 (27.1%) SPheo patients ($P=0.040$). 7 SPheo patients suffered tachycardia, five hypertensive crisis, one stroke, one acute pulmonary edema, one laceration, one died due to renal arterial injury and another one due to hypotension. Tumor recurrence rate was similar in both groups of patients (15.4% in FPheo and 11.3% in SPheo; NS)
Conclusion
FPheo usually appears in young patients with hypertension and family history of Pheo. In our series, FPheo was more frequently associated with MEN2A, with a multiple tumor presentation and smaller size compared to SPheo. Perioperative complications and recurrence rate seem to be similar in both groups. Genetic testing should be considered in all patients, especially in patients with a Pheo family history, young age, multifocal, bilateral and/or extra-adrenal tumors.

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P119

Clinical features, management and outcomes of adrenocortical carcinoma: a case series analysis

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Background
Adrenocortical carcinoma (ACC) is a rare and aggressive neoplasm with a 5-year survival rate $<$30%. Survival depends mainly on the stage at diagnosis, being surgery the only curative treatment.
Objective
To report the clinical features, management and outcomes of a series of ACC in two Spanish tertiary hospitals.
Material and methods
All patients with pathological diagnosis of ACC between 2000 and 2017 were included in this study. We herein report on data from clinical features, hormonal functionality, imaging, European Network for the Study of Adrenal Tumors (ENSAT) staging at diagnosis and response to treatment.
Results
We evaluated 28 patients (15 women, 53.6%) with a median age of 54.8 years [36–80]. Median tumor size was 12.1 cm [4–26]. Ten patients (35.7%) had hormonal overproduction: androgens in 10 patients, cortisol in 8 and mineralocorticoid in one. At diagnosis there were 16 patients (57.1%) in stage

IV, 8 (28.6%) in stage III, 8 (28.6%) in stage III and 4 (14.3%) in stage II. Four patients presented vena cava thrombosis. Surgery was performed in 26 patients, 20 of them with a complete resection. Twenty-four patients received mitotane (9 patients with concomitant chemotherapy, mainly cisplatin/etoposide, and one with concomitant chemoradiotherapy). Thirteen patients (54.2%) in stage IV, 7 (29.2%) in stage III and 4 (16.6%) in stage II. Thirteen out of 24 that received mitotane had disease progression and 9 died (8 in stage IV and one in III). Median daily dosage of mitotane was 2 g/day [1–10], with median treatment duration of 16 months [0–116]. Eleven patients (45.8%) suffered some adverse effect due to treatment and in 2 cases mitotane was withdrawn. Plasma mitotane levels were measured in 16 patients (66,7%). Appropriate therapeutic levels of mitotane were achieved in 57.9% of the measurments in 11 patients. Median follow-up of the patients was 27 months [0–316]. Eleven patients died: 9 in stage IV and 2 in III (6 of them with hypercortisolism). Two patients were lost for follow-up. In the group of the 15 surviving patients, 5 were in stage II at the diagnosis (one developed metastasis), 6 in III and 4 in IV.

Conclusions

One third of our ACC series were hyperfunctional, most of them multisecretory. Hypercortisolism could be a bad prognostic factor as well as the stage at the diagnosis. Mitotane can be a useful tool, but is mandatory to monitor plasma levels in order to get an effective response.

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P120

A case of multiple endocrine neoplasia type 1 (MEN1) with non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) responding to medical treatment with diazoxide

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Introduction

The non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) identifies a group of hyperinsulinemic hypoglycemic patients with unique clinical, diagnostic, surgical, and pathologic features. A selective arterial calcium stimulation test (SACST) with hepatic venous sampling can be performed to distinguish between a focal abnormality (insulinoma) and a diffuse process (islet-cell hypertrophy/nesidioblastosis). In patients with insulinoma, the response is positive in one artery alone unless the tumor resides in a "watershed" area fed by two arteries or the patient has multiple insulinomas scattered throughout the pancreas. In contrast, in patients with islet-cell hypertrophy, positive responses are usually but not always observed after injection of multiple arteries.

Case

A 50-year-old female previously had a parathyroid surgery and total gastrectomy; pathology revealed gastric neuroendocrine tumor (G-NET). The diagnosis was multiple endocrine neoplasia type 1 (MEN-1). She was admitted to our hospital for hypoglycemia. Her low fasting plasma glucose level (22 mg/dl), high insulin level (8.4 μU/ml), c-peptide level (2.3 ng/ml) were consistent with the possible presence of insulinoma. But an abdominal CT revealed no pancreatic tumor, and angiography of splenic artery showed no definite tumor stain within the pancreas, negative endoscopic ultrasound, negative octreotide scan and negative ^{18}F-DOPA PET. SACST was performed due to negative noninvasive imaging. Arterial stimulation and venous sampling showed an abnormal insulin response from superior mesenteric, gastroduodenal and splenic artery. The final diagnosis was adult-onset nesidioblastosis. The long-term therapeutic approaches for persistent hyperinsulinemic hypoglycemia may be accomplished pharmacologically or surgically. Pharmacologic interventions, although frequently unsuccessful, always should be tried before surgery. However, our case treatment with diazoxide at a starting dose of 200 mg/day dosage was gradually increased finally dose 400 mg/day resulted in amelioration hypoglycemia.

Discussion

Nesidioblastosis is a condition that can be seen in the majority of MEN1 patients with pancreatic involvement. Endogenous hyperinsulinemia may be due to single or more insulinoma, or it may also be due to diffuse hyperplasia, as seen in our case. The primary goal of therapy in nesidioblastosis is the prevention of acute neurologic symptoms (eg, seizure, lethargy, coma) and long-term sequelae (eg, cognitive deficits) of prolonged and/or recurrent hypoglycemia. The therapeutic strategies in nesidioblastosis include pancreatectomy and /or medical treatment. The initial treatment consists of nutritional management and use of diazoxide. This case report suggests that diazoxide may be effective for nesidioblastosis with MEN1 syndrome.

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P121

A case of benign insulinoma successfully treated with endoscopic ultrasound guided radiofrequency ablation

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Background

Insulinoma is a rare pancreatic neuroendocrine tumor but a life-threatening condition if untreated. Surgical resection is the standard of care with a high cure rate for benign insulinomas but complications can occur in nearly 30% of cases. New non-surgical mini-invasive ablative therapies can be considered in patients with benign insulinoma who are either unfit for surgery or refuse it, although current data are scarce and long-term outcomes are unknown.

Aim

We describe the case of a benign and small insulinoma successfully treated with endoscopic ultrasound (EUS) guided radiofrequency ablation (RFA).

Case description

A non-diabetic 69 year old woman presented with a 5 months history of recurrent episodes of sweating, tremor and refractory focal seizures despite levetiracetam therapy. During one of these episodes, a low capillary glucose level of 2.9 mmol/l was found with rapid normalization following glucose infusion. The patient was admitted to our hospital for a fasting test which confirmed the diagnosis of insulinoma based on the following laboratory findings: symptomatic low plasma glucose level of 2.5 mmol/l (normal range 3–5.6) within 28 hours of fasting, high plasma insulin and C-Peptide levels of 13.8 mU/l (3–13) and 2.6 ug/l (1.0–3.1) respectively. Screening for both sulphonylurea hyoglycaemic agents and circulating insulin antibodies was negative. Abdominal MRI and ^{68}Ga-DOTATATE PET CT were inconclusive. The EUS guided fine needle aspiration confirmed a 12 mm well differentiated G2 (Ki 67 $<$ 2%) neuroendocrine tumor located on the pancreas body. Symptoms of hypoglycemia were controlled with diet therapy. A multidisciplinary committee with the hepatobiliary surgery unit agreed to assess a minimally invasive endoscopic technique as an alternative to surgery. EUS-guided RFA of the pancreatic tumor was carried out using EUSRA^{TM} needle (19G, Teawoong). Apart from a mild transient fever that occurred 3 days after the procedure and treated with antibiotics, outcomes were favorable. The patient achieved symptomatic relief and biochemical normalization, and remained euglycemic during a follow-up of 2 months as confirmed by continuous glucose monitoring system.

Conclusion

This report adds to the emerging evidence of benign insulinoma being successfully treated by EUS-RFA, which may represent a potential alternative to surgery in selected cases. Further studies including larger patient samples are warranted to establish the safety and long-term efficacy of EUS-RFA in this setting.

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P122

Careful selection of patients with primary aldosteronism using combination of age, serum potassium and CT adrenal glands can avoid the need for adrenal venous sampling prior to adrenalectomy.

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Introduction
Adrenal venous sampling (AVS) is considered the reference standard to select patients with unilateral aldosterone producing adenoma for adrenalectomy. Recent studies debated the "mandatory" need for AVS before adrenalectomy. We report our experience from a tertiary hospital in Asia on the treatment outcomes of patients with primary aldosteronism (PA) who underwent adrenalectomy without AVS compared to those who had successful AVS.
Methods
A retrospective review of patients with PA who underwent adrenalectomy from February 2008 to July 2017 in Singapore General Hospital was conducted. All patients had positive case detection as defined by screening plasma aldosterone concentration (PAC): plasma renin activity (PRA) or active renin (DRC) of >20 or >3.8 respectively. They were further confirmed with intravenous salt loading test, with post infusion PAC >10 ng/dl (277 pmol/l). All patients with confirmed PA underwent adrenal CT scan. Clinical characteristics, CT findings and AVS results were analysed.
Results
In the entire cohort, 63.9% of patients had hypertension, 72.2% had hypokalemia and 16.7% had adrenal incidentaloma. Twenty three patients (63.9%) who underwent adrenalectomy had successful AVS while 13 patients (36.1%) were based on CT findings. The patients who underwent adrenalectomy based on AVS were older compared to those who did not have AVS, with mean age of 50.8 years and 45.9 years respectively. There was no significant difference in the level of hypokalemia in the AVS compared to the non-AVS group (2.7 mmol/l vs 2.9 mmol/l, $P=0.709$). Non-AVS based adrenalectomy group had an overall larger adrenal adenomas compared to the AVS based adrenalectomy group (2.23 cm vs 1.36 cm, $P=0.013$). There was no significant difference in the number of antihypertensive medications required prior to adrenalectomy in the non-AVS vs the AVS group (1.69 vs 2.17, $P=0.991$). When comparing between the non-AVS and the AVS-based adrenalectomy group, there was no significant difference in the patients who had complete resolution of hypertension (66.7% vs 45.5%, $P=0.678$) nor any difference in the reduction of anti HTN medications (45.5% vs 36.4%, $P=0.079$). In the non-AVS group, the factors associated with improvement in hypertension, were age <45 years ($P=0.014$), adrenal adenoma size ≥ 1.3 cm with contralateral normal adrenal gland on CT scan ($P=0.028$) and K <3.2 mmol/L ($P=0.028$). Among those did not experience improvement in hypertension after adrenalectomy, all were $>$ 45 years old.
Conclusion
Where access to expert AVS is limited, adrenal CT combined with specific clinical and biochemical features can potentially safely select patients for adrenalectomy.

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P123

Hormonal secretion prevalence in a series of subjects with adrenal tumors incidentally discovered in clinical practice

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The objective of the study was to evaluate the prevalence of secreting profile among a series of subjects with incidental discovered adrenal tumors. Subjects. 139 subjects (112 women and 27 men) diagnosed with adrenal tumors between 2010 and 2015 in our department.
Methods
Medical records were retrospectively analysed for demographic data, routine tests, specific adrenal hormones measurements, associated diseases.
Results
Regarding the tumor localisation, 46.5% of the subjects had left adrenal tumors, 31.5% on the right adrenal gland and the other had bilateral tumors. Forty out of all subjects (28%) had a positive test for an adrenal hormonal secretion according to diagnosis tests criteria for either cortisol, cathecolamines or aldosterone: 87% for cortisol, 8% for cathecolamines and 5% for aldosterone. Measurements of the adrenal hormones were not done routinely in all subjects, presence of high blood pressure in a young patient beeing a selection criteria in the majority of the cases. On the other hand cortisol secretion evaluation was the most affordable and accesible measurement in the studied clinical setting; thus it was done in all the subjects. Cathecolamines and aldosterone secretion was evaluated in less than 20% of the subjects.The secretory characteristic of the tumors was significantly correlated to bilateral tumors (85% vs 68% on right or 47% on the left). A significantly increased diameter of the tumor (2.7 cm) was found in secretory ones vs non secretory (2.2 cm, $P<0.05$) No significant correlations were found between positive hormonal secretion of the tumors and gender, localisation, BMI, age, associated diseases. Conlcusion. Twentyeight percent of the patients with and incidental discovered adrenal tumor had a positive secretory profile wich was associated to a greater diameter of the tumor and bilateral localisation. The most frecvent found secretion was cortisol, finding which is most probable biased by a more available measurement.

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P124

Genetic background as a predictive factor of pheochromocytoma and paraganglioma presentation

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Introduction
Pheochromocytoma (Pheo) and paragangliomas (PGL) are rare catecholamine-producing tumors.Near 35% of patients have disease-causing germline mutations.10% are malignant although the malignancy rate differs accordingly to the genetic background.
Purpose
This study aims to characterize the sample of patients followed on a tertiary Portuguese Center and associate the presence of genetic mutation with clinical presentation.
Materials and Methods
Were included patients followed until November 2017 with proven histological diagnose.Statistical analysis was performed with SPSS v.25 –Fischer test: nominal variables and U de Mann-Whitney test: ordinal variables. Results with $P<0.05$ were considered statistically significant.
Materials and Methods
*Results:*We included 67 subjects (65 with disease; 2 asymptomatic carriers of exon 2 mutation of *TMEM127* gene). From the 65 patients, 60 had Pheo, 3 head-and-neck PGL and 2 abdominal PGL. In 12.3% of the patients (8/65) evidence of metastatic disease was reported, of which 87.5% (7/8) identified at diagnose. The most frequent local of metastatic disease was bone (71.4%).7 patients died during follow-up (10.8%), 2 with previously known metastatic disease (1 Pheo;1 parapharyngeal PGL).Our sample was divided in 3 groups: negative genetic test (GT) ($n=30$; 28 Pheo); positive GT ($n=17$; 14 Pheo) – cluster 1 genes: 4 patients (*VHL*−3; *SDH* gene-1) and cluster 2 genes: 13 patients (*RET*-7; *TMEM127*−4; *NF*-2); unavailable GT ($n=20$; 10 Pheo). Compared with patients with negative GT, patients with positive GT were significantly associated to larger tumors (66.62 ± 35.8 mm vs. 44.57 ± 20.0 mm; $P=0.031$), bilateral disease (6 (40%) vs. 1 (3.3%); $P=0.003$), earlier age at diagnose ($<$ 40 years: 9 (60%) vs. 6 (20%); P 0.017) and positive familiar history (8 (53.3%) vs. 1 (3.3%); $P<0.001$). Regarding to recurrence, the mean time (months) elapsed was lower in the positive GT group (4.40 ± 15.5 vs. 7.53 ± 23.5) without reaching a statistically significant difference ($P>0.05$). There were no significant differences on clinical presentation, suggestive imagiological characteristics on anatomical (CT or MRI scan) or functional techniques (^{123}I-mIBG scan) ($P>0.05$).
Conclusions
In our sample, 1/3 of patients with history of Pheo/PGL presented a positive GT and near 12% showed metastatic disease, similarly to the data published in the literature. From the positive GT group, 93.3% were Pheo cases accordingly to the most frequent gene mutations identified – cluster 1: 3 patients with *VHL* mutations and cluster 2:13 patients. In this group, we also found a stronger association to bilateral disease, manifestation $<$40 years of age, positive familiar history and larger tumors.

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P125

Heterogeneous genetic background of Hungarian patients with pheochromocytoma/paraganglioma requires gene panel testing

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Introduction
Pheochromocytomas and paragangliomas (Pheo/PGL) are rare neuroendocrine tumours arising from the adrenal medulla or the symphathetic paraganglia, respectively. Germline mutations are present in ~40% of the patients. To date, at least 16 genes have been demonstrated to be involved in the genetic background of Pheo/PGL. Prioritization in order of genes tested can be applied, but if the probability of a disease-associated germline mutation exceeds 10% the testing of all susceptibility genes is recommended. Using next generation sequencing (NGS) based methods for genetic testing of Pheo/PGL associated genes progressively becomes part of the routine diagnostics.
Objective
To assess the genetic background of Hungarian patients with Pheo/PGL and to develop a NGS based gene panel assay for analysis of Pheo/PGL susceptibility genes.
Methods
We examined 131 patients with the diagnosis of Pheo/PGL diagnosed and nursed at the 2nd Department of Medicine, Semmelweis University. The prevalence of the germline mutations of Pheo/PGL genes was determined using conventional methods. Genotype-phenotype correlations were evaluated. A gene panel covering 15 genes (*RET*, *VHL*, *NF1*, *EPAS*, *EGLN1*, *KIF1B*, *SDHA*, *SDHB*, *SDHAF2*, *SDHC*, *SDHD*, *FH*, *MAX*, *TMEM127*, *MEN1*) was developed and analytical sensitivity was evaluated on 36 patients with known genetic background. Library preparation was performed using SeqCapEZ capture platform with our probe design. Illumina MiSeq instrument was used for sequencing. Sequencing data were analysed with GATK workflow. Variant annotation was performed with SNPeffect.
Results
Germline mutations of Pheo/PGL genes were present in at 34% of the patients: 10 (7.6%) *SDHB*, 9 (6.9%) *RET*, 5 (3.8%) *VHL*, *TMEM127*, *MDH2*, 4 (3%) *NF1*, 3 (2.3%) *SDHD*, 2 (1.5%) *SDHC* and *KIF1B*. 5 of 10 *SDHB* mutation carriers developed malignant disease. Homozygous form of a *MDH2* variant was associated with malignancy. Among the 10 patients with bilateral adrenal Pheo 4 *RET*, 2 *TMEM127* and 1 *VHL* mutations were identified. The coverage of genes in our panel was higher than 150 reads in all regions and all known mutations were correctly identified.
Discussion
Our findings regarding the prevalence of germline mutations in the development of Pheo/PGL are in accordance with the literature. No founder mutation occurred in our population as we could detect mutations in 9 genes, underlining the need of novel methods for mutation analysis in everyday clinical practice. Our NGS-based gene panel performed accurately, however two recently identified genes (*MDH2*, *GOT2*) were not covered.

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Gastroenteropancreatic neuroendocrine tumors are predictive for a positive *MEN1* germline mutation test: evidence from Hungarian MEN1 cohort

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Objective
Multiple endocrine neoplasia type 1 (MEN1) is a rare heritable tumor syndrome caused by germline mutations of *MEN1* gene affecting mainly the parathyroid, pituitary and pancreas. Phenotype varies widely, even in first-degree relatives. Recently it has been shown that functionally active gastroenteropancreatic neuroendocrine tumors (GEP-NETs), initially frequently diagnosed as sporadic cases, lead to MEN1 diagnosis. Non-functioning tumors are increasingly recognised due to advanced imaging modalities such as endoscopic ultrasound and thus became the most common GEP-NET in MEN1 patients. Contrary to sporadic GEP-NETs, MEN1-associated cases are diagnosed 10 years earlier and their penetrance is as high as 80-90%, reaching nearly that of the parathyroid adenomas. Mutation analysis enables early tumor detection, thus the possibility to prevent serious, even life-threatening morbidities associated with malignant GEP-NET. Our aim was to identify phenotype features predictive for a positive *MEN1* genetic test, and by comparing mutation-positive and mutation-negative patients to evaulate the role of *MEN1* mutations in phenotype modulation.
Design and methods
Of the 104 probands who fulfilled the criteria of *MEN1* mutation analysis, 36 patients with GEP-NET were enrolled in this study. Mutation screeening of the *MEN1* gene by Sanger sequencing was performed at our national reference laboratory. Clinical data were studied together with laboratory, imaging and histological results. Multiple ligation probe amplification analysis of *MEN1* gene and Sanger sequencing of *CDKN1B* were carried out in clinically suspicious but *MEN1*-negative cases.
Results
Of 36 GEP-NET patients mutation analysis demonstrated disease-causing mutation in 19 patients. GEP-NET developed significantly earlier in mutation-positive patients; more than half of them appeared under 30 years of age. The prevalence of GEP-NET was also significantly higher at initial presentation in mutation carriers compared to mutation negative patients. The presence of GEP-NET under 30 years best predicted a positive *MEN1* genetic test. Its prevalence remained significantly higher among mutation carriers during the follow-up. In addition, probands with high-impact mutations (frameshift, nonsense, large deletions), predicted to affect menin function significantly, developed GEP-NETs more frequently compared to low-impact (inframe and missense) mutation carriers.
Conclusions
GEP-NETs appear significantly earlier and more frequently in *MEN1*-positive patients and best predicted a positive genetic test. MEN1 patients with high-impact mutations were more likely to develop GEP-NETs, revealing a possibly important prognostic consequences regarding genetic counseling.

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Adrenocortical cancer – the effectiveness of mitotane therapy depending on the time of therapy and the therapeutic dose

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Introduction
Mitotane-o'p-DDD belongs to insecticides (DDT pesticide contamination), it is the only drug registered by the FDA in treatment in adrenocortical carcinoma (ACC). Treatment effect is controled by mitotane concentration in the blood.
Aim
The aim of the study is to evaluate the effectiveness of mitotane treatment in patients with adrenocortical cancer.
Material and methods
We retrospectively reviewed data on ACC patients ($n=204$) treated with o,p′DDD ($n=117$) between 2002 and 2017. Finally, a total number of 55 patients was included in the study. In these patients, we analysed a graph of mitotane concentrations during the course of therapy. Therapeutic window of mitotan was set according to the characteristics of the medicinal product (FDA) at 14-20 mg/l. Patients were divided into two groups. For the study group, the inclusion criterion was to maintain the concentration window of mitotane in the plasma least at 50% of the treatment time. The study group included 17 people (31% of patients) The comparative group group consisted of those who did not reach the therapeutic window, 38 patients (69%). We observed patients from both groups in time one year intervals after the inclusion of mitotane therapy. In the evaluation of the effectiveness of the therapy, we based on the comparison of subsequent CT and MR results according to RECIST criteria. Average duration of treatment was up to 40 months in the first group of patients Average duration was of treatment was up to 28 months in the second group of patients.

Results
After a year 60% exhibited the stable disease. In the study group of patients, we observed stable disease in 82% of patients who is 23% ($N=4$) of patients had regression of the disease ($P<0,05$). In comparative group – stable disease was observed in only 50% of patients.
Conclusion
In conclusion, our data confirm the value of o,p′DDD plasma monitoring with ACC patients. Furthermore, our results suggest additional benefit of a targeting the o,p′DDD in terapetic window which has to be confirmed in a prospective study. In view of the limited possibilities of other therapies, the discussion on the use of mitotane remains open.

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Ghrelin is overexpressed in adrenal cancers and stimulates proliferation and migration of ACC cell line.

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Purpose
Adrenal cancers are relatively rare, but they have poor prognosis. IGF2 has been confirmed as a factor of adrenal tumors development. Recent data indicate that ghrelin may be an essential factor in cancerogenesis. The aim of our study was to assess ghrelin expression in adrenal tumors, and to investigate the relationship between ghrelin, IGF2 and the clinicopathological characteristics. We also investigated the influence of ghrelin on adenocarcinoma cell line proliferation in *in vitro* analysis.
Materials and methods
The study group included 77 patients diagnosed with adrenal tumors, qualified for adrenalectomy. All patients underwent physical examination, laboratory testing, and computer tomography scan before the operation. Expression of ghrelin and IGF2 in adrenal tumors: 30 adenoma, 12 hyperplasia, 8 myelolipoma, 20 pheochromocytoma, 7 carcinoma and 7 unchanged adrenal glands were estimated with RT qPCR. All parameters were compared in examined groups and correlations between them were estimated. H295R cell line was stimulated by ghrelin to assess proliferation and migration.
Results
We found ghrelin overexpression in adrenal cancers, while the lowest level of ghrelin expression was observed in the control group. Ghrelin expression was 21 times higher in carcinoma ($P=0.017$); 2.4 times higher in adenoma ($P=0.029$). There were no statistical differences between myelolipoma ($P=0.093$) and pheochromocytoma ($P=0.204$) in relation to control. Ghrelin was statistically higher in carcinoma compared to adenoma ($P=0.049$). The positive correlation between ghrelin and IGF2 expression was observed only in myelolipoma ($P=0.001$). Ghrelin in concentrations of 1×10^{-6} M and 1×10^{-8} M significantly stimulated proliferation and migration in the H295R cell line.
Conclusion
Ghrelin may be involved in adrenal tumors development.

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The effect of temozolomide on pancreatic neuroendocrine tumours and role of MGMT and MMR system in temozolomide resistance

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Background
Temozolomide (TMZ) has been suggested as a treatment option for patients with pancreatic neuroendocrine tumours (PNETs). The tumour response to TMZ has been linked to expression levels of O6-methylguanine-DNA methyltransferase (MGMT) and components of the mismatch repair (MMR) system. However, there is no *in vitro* data on TMZ sensitivity and the expression of MGMT and MMR components in PNETs. Moreover, the effect of TMZ exposure on chemosensitivity and expression of MGMT and MRR components in PNET cell lines is unknown.
Methods
Two PNET cell lines, BON-1 and QGP-1, were used to determine TMZ sensitivity. TMZ resistance was induced by exposing cells to three 24-hour challenges with increasing doses of TMZ, each followed by a two week drug-free period. The effect of TMZ on cell growth, transcription of *MGMT* and MMR components (*MLH1, MSH2, MSH6, PMS2*), apoptosis induction and cell cycle was assessed.
Results
BON-1 were more sensitive to TMZ, compared to QGP-1, as reflected by a lower IC50 value of TMZ on cell growth ($P<0.001$). After a 24-hour exposure to 1x IC50 dose of TMZ, BON-1 cells develop TMZ resistance and maintain this phenotype. TMZ resistance was associated with increased *MGMT* expression and a decrease in TMZ-induced apoptosis and cell cycle arrest. In contrast to BON-1, the less TMZ sensitive QGP-1 cells have a higher base-line *MGMT* expression. Moreover, exposure of QGP-1 to TMZ did not result in increased resistance. In both cell lines, there was comparable expression of MMR components and exposure to TMZ was not associated with a shift in expression levels.
Conclusion
We demonstrated that TMZ sensitivity in human PNET cells is associated with the expression of *MGMT*. Furthermore, a single, short-term exposure to TMZ can induce sustained resistance in TMZ sensitive cell lines which is associated with increased *MGMT* expression.

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Treatment with (177Lu)-dotatate in patients with advanced metastatic somatostatin receptor-positive tumors

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Introduction
The NETTER 1 trial resulted in markedly longer progression-free survival (PFS), with preliminary evidence of an overall survival benefit. We report the results of PFS and safety of (177Lu)-DOTATATE in patients treated in our hospital between 2014 and 2017.
Methods
Transversal and descriptive study of 22 patients with advanced, progressive, somatostatin receptor-positive tumors who had received previous treatments. All of them were treated with (177Lu)-DOTATATE. Results are expressed in average(SD) or percentage (%). SPSS version 2.2 was used for statistical analysis.
Results
59.1%(13) were women, with an average age of 53.32(15.2). Histological classification was: 16(72.7%) well-moderate differentiated neuroendocrine tumors (NETs) (8 pancreatic, 4 midgut, 2 lung and 2 unknown primary), 5(22.7%) paragangliomas and 1(4.5%) follicular thyroid carcinoma. At the time of administration of (177Lu)-DOTATATE, 21 patients were in metastatic stage, and one had unresectable bilateral neck paragangliomas. The localization of the metastasis was: liver 68.2%(15), bone 45.5%(10), lymph nodes 27.3%(6) and lungs 9.1%(2). All patients had received previous treatments: 2 underwent surgery exclusively, 4 were treated with somatostatin analogues (SA), 4 with SA and surgery, and the rest of patients with another systemic therapies in addition to SA and surgery: tyrosine-kinase inhibitors, mTOR inhibitors, and standard chemotherapy. 177Lu-DOTATATE was infused every eight weeks. 16 patients have already finished the treatment: 14 patients received 4 doses (59.1%), 2 received only 3 due to the excellent response. Three patients have not received yet complete treatment, and finally 3 remaining patients died during the treatment. At the data-cutoff date PFS was of 12.86(12.43) months. Ten (45.5%) patients had adverse events related to the treatment: 1 asthenia, 4 self-limited nausea, vomiting or abdominal pain, and 5 haematologic events (3 mild-moderate anemia, 2 pancytopenia, one of them with fatal ending). During the follow-up, 5 patients have died.

Conclusions
In real world practice, treatment with (177Lu)-DOTATATE not only shows benefit in advanced intestinal NETS but also in other patients with metastatic disease, previous treatments, and positive somatostatin-receptor expression. 177Lu seems to have favorable results attending to PFS and safety.

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Severe impairments in health-related quality of life in patients with small intestine neuroendocrine tumors

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Background
The prevalence of small intestine neuroendocrine tumors (SI-NETs) is increasing. Disease progression is often slow, treatment options and long-term survival rates have improved. Health-related quality of life (HRQoL) is considered an important measure of patients' perception of the burden of their disease and the impact of treatment modalities. Despite this, data on whether improvements in treatment options and survival rates also translate into improved HRQoL in patients with SI-NETs are scarce.
Objective
To assess HRQoL and its predictors in carefully characterized SI-NET patients, and compare the results to that of a general population in Finland.
Design
We studied HRQoL with 15D and SF-36 questionnaires in 134 grade 1 and 2 SI-NET patients and compared 15D results to those of age- and gender-standardized general population ($n=1153$). Patients with histologically confirmed diagnosis of SI-NET treated at the Division of Endocrinology and Department of Oncology of the Helsinki University Hospital during year 2017 were included in the study. We studied whether socioeconomic factors, disease characteristics including treatment modalities, medication and/or comorbidities predicted HRQoL.
Results
Mean disease duration was 81 (4–468) months, 91% had metastatic disease and 79% received somatostatin analog treatment. Hepatic tumor load was 0% in 44.8%, <10–25% and >25% in 44% and 11.2%, respectively. Ki-67 was 3.7 (0.5–15) %. Mean fP-CgA and S-5HIAA concentrations were 15 (1.3–250) and 344 (24–7470) nmol/l, respectively. Overall HRQoL was significantly impaired in patients compared to controls (total 15D scores 0.864 ± 0.105 vs 0.905 ± 0.028, $P<0.001$). SI-NET patients scored worse on 9 of 15 dimensions (sleep, excretion, depression, distress, vitality, sexual activity ($P<$ 0.001), breathing, usual activities and discomfort and symptoms ($P<$ 0.01–0.05). SF-36 dimension scores correlated highly with total 15D score ($P<0.001$). Patients with low 15D score in excretion dimension (impaired excretion, $n=85$) had significantly impaired HRQoL compared to those ($n=49$) without impaired excretion (0.828 vs 0.933, $P<0.001$). Diarrhea, depression and number of medications independently predicted impaired HRQoL. In contrast, age, gender, educational level, Ki67 index, hepatic tumor burden, S-5HIAA, cardiovascular or diabetes comorbidity, somatostatin analog or interferon therapy or peptide receptor radionuclide therapy did not predict HRQoL.
Conclusions
Overall HRQoL is severely impaired in SI-NET patients. The most affected dimensions are excretion, sleeping, depression, distress, vitality and sexual activity. Improved treatments of diarrhea and depression are warranted.

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Role of GLUT-2 expression and MGMT methylation for streptozotocin clinical response in adrenocortical carcinoma

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Introduction
Streptozotocin (SZ) is an active drug for the treatment of advanced adrenocortical carcinoma (ACC) in a minority of patients with an objective response rate of <10%. It has been reported that expression of glucose transporter-2 (GLUT-2) is essential for SZ to enter tumor cells and that high activity of O-6-methylguanine-DNA methyltransferase (MGMT) counteracts the alkylating effect of SZ. Therefore, we aimed to clarify the role of GLUT-2 and MGMT in the response of ACC to SZ.
Methods
GLUT-2 membrane protein expression was analyzed by immunohistochemistry in paraffin embedded tissue sections from 78 ACC patients (28 SZ responders and 50 with progressive disease). Methylation status of the promoter regions of MGMT and DNA mismatch repair (MMR) genes MLH1, 3, MSH2, 3, 6; PMS2 was assessed by multiplex ligation–dependent probe amplification (MLPA) using corresponding tumor and germ line DNA and compared with methylation of the same promoter in 6 normal adrenal glands.
Results
Membrane-located GLUT-2 protein was detected in all patients with objective response after SZ treatment and in 46/50 (92%) of the non-responders, without significant difference in average expression levels. Analysis of the samples with GLUT-2 membrane expression for promoter hypermethylation revealed significantly higher MGMT promoter methylation in responders than in non-responders ($P=0.02$) while other MMR gene promoters showed higher methylation in non-responders ($P=0.03$). MGMT hypermethylation was strongly associated with improved progression free survival during SZ (unmethylated: 3.9 ± 1.7 months; hypermethylated: 5.1 ± 0.8 months, $P=0.06$) while hypermethylation of MMR gene promoters was strongly associated with progression-free survival independent of treatment (unmethylated: 8.79 ± 2.3 months; hypermethylated: 19.23 ± 8.2 months, $P=0.05$).
Conclusion
These data demonstrate that GLUT-2 expression is necessary but not sufficient for therapeutic response to SZ in ACC. MGMT promoter hypermethylation is strongly associated with clinical efficacy of SZ, while hypermethylation of 6 other MMR gene promoters is associated with less aggressive tumors. This may be related with their role in creating neo-antigens similar to other solid cancers.

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Presence and functional role of KiSS/KiSS-R system in pancreatic neuroendocrine tumors (panNETs) and its relationship with clinical features and tumor behavior

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Pancreatic neuroendocrine tumors (panNETs) are the second most common neoplasm of the pancreas. panNETs arise from cells of the pancreatic islets and

comprise a diverse and heterogeneous group of neoplasms. This hampers their systematic study, and the identification of common molecular signatures that might facilitate a better diagnosis of the disease, and the development of efficient therapeutic approaches. Indeed, there are no clinical, biochemical, anatomopathological, immunohistochemical or molecular features capable to predict either tumor prognosis or postsurgical treatment for panNETs. Current evidence indicate that certain regulatory systems composed of G-protein coupled receptors and their ligands could play a crucial role in the development and/or progression of different endocrine-related tumors. In this line, several studies have shown that the KiSS/KiSSR system is present in certain tumor types where it exerts antitumoral actions. Accordingly, the goal of this study was to determine the presence of this system in human panNET tissue samples by qPCR ($n=46$, including tumor and non-tumor adjacent regions) and to analyze its relationship with several tumor distinctive clinical features related to tumor prognosis. In addition, we sought to study the potential functional role of this regulatory system in panNETs using BON1 cell line. Firstly, we found that expression levels of KiSS were higher and of KiSSR lower in panNET tissues compared to its adjacent non-tumor tissues. Moreover, KiSS expression appeared to be upregulated in panNET samples from patients harboring metastatic disease, whereas KiSSR expression was significantly lower when compared to samples from non-metastatic patients. In addition, functional assays demonstrated that kisspeptin10 significantly modulated both cell proliferation and migration processes in BON1. Interestingly, blockade of KiSSR using a KiSS1R-antagonist (kisspeptin234) evoked a significant increase in the proliferation rate of panNET cells after 24 and 48 h, while did not change cell migration capacity. Finally, combined administration of kisspeptin10 and KiSS1R-antagonist significantly reduced BON1 cell proliferation and migration after 24 h exposure, suggesting that KiSS1R-antagonist did not counteract the antitumoral action of KiSS1 in this experimental setting. Ongoing analyses indicate that the antitumor actions of KiSS1 on panNET cell line involve the modulation of various signaling pathways and different molecular mechanisms. Altogether, our results provide original evidence for the presence and functional activity of the KiSS/KiSSR system in panNETs, suggesting its potential role in the development and/or progression of this pathology, and paving the way to explore its value as a novel biomarker and/or therapeutic target in panNETs.

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Mesenchymal tissue markers as potential drug targets in adrenocortical tumours

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Introduction
Adrenocortical carcinoma (ACC) is a rare, aggressive tumour with unsatisfactory treatment options in advanced disease. Activation of epithelial to mesenchymal transition (EMT) has been described as causative of metastatic spread in a variety of human cancers. Accordingly, new drugs were developed specifically targeting EMT with a focus on HGF/c-MET and FGF/FGFR signalling. We here asked whether EMT is a relevant mechanism in ACC.
Methods
Expression of epithelial and mesenchymal markers was assessed in 20 normal adrenal glands (NAG), 23 adrenocortical adenomas (ACA) and 27 ACC. Epithelial marker E-cadherine and mesenchymal markers SLUG and N-cadherine were analysed by IHC. Expression of FGFR1-4 was quantified in FFPE tumour tissue using RNAscope and qRT-PCR array was employed to quantify expression of 92 FGF-FGFR pathway genes. Isoform switching between isoforms IIIb (epithelial) and IIIc (mesenchymal) characteristic for EMT was assessed for FGFR 1 and 2 by qRT-PCR with specific primers. c-MET was quantified by qRT-PCR and IHC.
Results
Surprisingly, all adrenal tissues lacked E-cadherine expression while N-cadherine was present in both normal and neoplastic adrenal tissues but was significantly lower in malignant vs benign tissues (0.88 ± 0.16 vs 1.64 ± 0.19, $P=0.007$). SLUG had a uniformly high nuclear expression in all adrenal tissues. FGFR2 mRNA was expressed at lower levels in ACC compared to ACA (3.1 ± 2.1 vs 6.5 ± 2.3 mRNA copies/cell, $P=0.0005$) whereas FGFR1 (7.5 ± 5.3 vs 4.5 ± 2.9, $P=0.09$) and FGFR4 (5.1 ± 2.3 vs 2.6 ± 1.3, $P=0.002$) were higher in ACC. FGFR4 expression was higher in advanced (ENSAT stage 3 and 4) vs localized ACC (6.2 ± 1.6 vs 3.9 ± 2.7, $P=0.03$). FGF/FGFR pathway analysis confirmed differential FGFR expression and revealed decreased expression of FGF7, FGF17 and mitogen associated protein kinases in tumors compared with NAG. Surprisingly, all adrenal tissues had higher expression of IIIc vs. IIIb isoform expression of both FGFR1 and 2. c-MET expression was significantly higher in ACC compared to ACA and NAG at mRNA but not protein level.
Conclusions
Normal adrenal cortical tissue but also adrenocortical tumors exhibit consistent expression of proteins considered to reflect mesenchymal differentiation. This is probably due to their origin in the intermediate mesoderm. However, significant changes in expression of mesenchymal marker N-cadherine and FGF/FGFR system suggest their relevance in adrenocortical tumorigenesis and progression. Receptor tyrosine kinase FGFR4 may be also a suitable treatment target for advanced ACC.

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P135

Multiple endocrine neoplasia type 1: a retrospective monocenter analysis of 73 cases

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Multiple endocrine neoplasia type 1 (MEN1) is an inherited syndrome, affecting multiple endocrine glands whose natural history remains largely unknown. Aim of this study was to assess the epidemiological and clinical profile of MEN1 in a single center. Seventy-three MEN1 patients, belonging to 30 different families, referred at the NET Center of Naples, from 2000 to 2017, were evaluated. Male/female ratio was 0.73, mean age 43 years (range 10–86). Forty-six cases (64%) were diagnosed on family screening. A MEN1 gene mutation was found in 67 cases (92%) and deletion in 1 case. Primary hyperparathyroidism (PHPT) was the most common manifestation (86%), followed by duodeno-pancreatic neuroendocrine tumor (DP-NET) (74%) and pituitary adenoma (PA) (45%). Seven subjects (10%), mean age 22.7 years (range 10-34), have not yet presented any manifestation of MEN1, whereas 26 patients (36%) developed PHPT, DP-NET and PA. DP-NET were mostly non functioning (76%), followed by gastrinoma (22%), insulinoma (2%). Metastases occurred in 7 (13%), four of whom had exon 2 frameshift mutations. Five patients (7%) died, 2 for liver insufficiency of DP-NET, 1 for renal insufficiency, 2 due to DP-NET postoperative complications. Twenty-nine DP-NET patients (54%) received therapy with somatostatin analogs. Two were treated with targeted agents. Median overall survival in DP-NET patients was not reached. Among PA, 42% were macroadenoma, 45% were prolactinoma. Adrenal hyperplasia was found in 29%, mostly hormonally silent (86%), except 1 pheochromocytoma, 1 aldosterone-producing, 1 glucocorticoid producing adenoma. Five patients (7%) developed bronchial/thymic carcinoid. These data contribute to clarify the clinical picture of MEN1. Peculiar finding of our cohort is the high prevalence of DP-NET and adrenal lesions, due to better screening methods.

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P136

Cell line derived from glioblastoma synthesizes steroid hormone. Effect of enzyme inhibitors

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Glioblastoma (GB) is the most aggressive primary brain tumor, the survival rate is low because of a high prevalence of recidives. The incidence of GB in the adult

population is 50% higher in men than in women, which suggest a role of steroid hormones in it is development. Information on GB as a steroidogenic tissue is poor. The objectives of this study were: 1, to investigate the capacity of a human GB cell line to synthesize sex steroids and corticosteroid metabolites, and 2, to know the effects of two enzymatic inhibitors of 5-alpha reductase, finasteride and dutasteride, on the hormonal metabolism of the tumoral cells. U87GB cells line were cultured with DMEM, antibiotics and 10% FBS. Thereafter media were replaced by fresh culture media without FBS. Tritiated steroid precursors, progesterone (^{3}H-P4) or androstenedione (^{3}H-A_4), were added to the media and cells cultured in the presence or absence of three concentrations of finasteride or dutasteride. Culture media were collected after 24 or 48 h, and extracted with ether. The resulting steroids were separated by thin layer chromatography (TLC). Data were expressed as percent transformation of the tritiated precursors ± S.E. Results showed that the U87 cells incubated with ^{3}H-A_4, synthesized significant quantities of testosterone after 24 h. The synthesis decreased by 48 h, but the production of its metabolites, dehidrotestosterone (DHT) and androsterone increased. After 48 h finasteride inhibited the production of DHT, dehidroandrosterone (DHA), androsterone and androstanedione. After 48h of culture dutasteride significantly inhibited the synthesis of the testosterone metabolites DHT, DHA, androsterone and androstanedione. The incubation of U87 cells with ^{3}H-P4 for 24 and 48 h lead to the time-dependent synthesis of the corticosteroid metabolites 17-hydroxyprogesterone (17-OHP4), deoxycortisol (DCLS), deoxycorticosterone (DOC), cortisol (CLS), corticosterone (CNE) and aldosterone. The addition of dutasteride to the culture media caused the inhibition of the synthesis of CLS, DCLS, aldosterone, allocorticosterone, and dehidrocorticosterone (DHC) with a significant accumulation of DOC after 48h of culture. In conclusion, U87 cells have the capacity to synthesize sex steroid hormones and corticosteroids, with a remarkable abundance of androgens. 5-alpha reductase inhibitors significantly reduced the synthesis of androgenic metabolites. In addition, dutasteride blocked the 5-alpha reductase action on the corticosteroid pathway, affecting the metabolite synthesis. Therefore, 5-alpha reductase inhibitors may possibly have a role in the control of GB.

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P137

Unraveling the incidence and clinical patterns of neuroendocrine neoplasms in Greece, through the experience of multipotent, specialized clinical centers.

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Introduction
Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors arising from neuroendocrine cells in the endocrine and central nervous system, the natural history of which remains inadequately understood. Large epidemiological studies are gradually emerging from different countries worldwide, which contribute to the establishment of a spherical view about these tumors. The purpose of this study is to evaluate the epidemiological, clinical and pathological characteristics of patients with NENs that have visited the specialized, multipotent medical center of a University Hospital in Athens, Greece.
Methods
311 patients with NENs were recruited at the specialized, outpatient Medical Center of Neuroendocrine Tumors of the Endocrine Department of 'Sotiria' University Hospital in Athens, Greece, during the period from September 2013 till the end of 2014. Anthropometric, clinical, laboratory, imaging and pathologic data were obtained from every patient.
Results
55.9% of patients with NENs were female and 44.1% were male. The mean age at the time of diagnosis was 52.77 ± 16.7 years old. The majority of NENs were detected in the gastroenteropancreatic system. The most common primary site was stomach (23.8%), followed by pancreas (19.6%) and appendix (12.9%). In 31 patients (10%) the primary tumor remained unknown. Over half of NENs were regional at the time of diagnosis, 18.6% of patients had locally extended disease, while 25.4% of NENs, involving mostly NENs of unknown origin, pancreas and small intestine, were metastatic. Simultaneously, most of them displayed a Ki-67 index of ≤2%, while G3 classification, with a high proliferation index was only observed in pancreatic, rectal and rare NENs. Laboratory data revealed that CgA can predict whether a NEN is metastatic or not, but cannot predict how aggressive its behavior can be. On the contrary, NSE cannot be used as prognostic marker both in disease extent and grading of NENs. Finally, it was observed that patients with CgA levels in the highest quartile (CgA > 237 ng/ml) displayed 8 times higher risk for being metastatic at the time of diagnosis (OR = 8.643, 95% CI = 2.576–9.0).
Conclusions
This is one of the first large, epidemiological studies in Greece, evaluating the natural course of NENs through the experience of a specialized medical center. NENs of the gastroenteropancreatic system were most common, mainly regional at the time of diagnosis and with a Ki-67 index of ≤ 2%. CgA can be a useful marker in predicting disease extent of NENs.

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P138

Evaluation of neurofibromatosis type 1 and gastroenteropancreatic neuroendocrine tumors.

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Introduction
Neurofibromatosis type 1 (NF1) is an autosomal dominant condition with an incidence of 1 in 2600 to 3000 individuals. Patients with this disorder are characterized by multiple neurofibromas, caf-au-lait macules, axillary freckling, optic gliomas, iris hamartomas, and skeletal abnormalities. Overall risk of developing neoplasms is approximately 2 to 4-fold higher in patients with NF1, with a risk of malignancy estimated between 5 and 15%. Endocrinopathies are sometimes associated with this condition. Patients with NF1 usually assessed at Endocrinology consultation are those who suffer from gastroenteropancreatic neuroendocrine tumours (NET) (∼1.0%) and/or pheochromocytomas/paragangliomas (∼0.1-5.0%). Gastroenteropancreatic involvement in NF1 includes gastrointestinal stromal tumors (GIST), carcinoids, somatostatinomas, gastrinomas, insulinomas and nonfunctioning pancreatic tumors.
Methods
We identified 11 patients with NF1 who are still ongoing follow-ups at the Endocrinology Service of our Centre. Of those, two were found to be affected by NETs. We describe the demographic characteristics, the age of diagnosis, the type of tumor and its current status.
Results
Case 1. A 58-year-old woman that underwent an enucleation of a pancreatic somastotatinoma at the age of 15. She has non-specific lesions in the liver, but none with evidence of metastases and on the other hand has high chromogranin a (CgA) levels, therefore she is being treated with a somatostatin analogue.
Case 2. A 70-year-old man proceded to a pancreatoduodenectomy of a dudodenal somastotinoma at the age of 67. The tumor size was 25 mm and the average Ki67 < 5%. There is currently no evidence of metastases and CgA levels are normal.
Conclusions
Although association of gastroenteropancreatic NETs in the context of patients with NF1 is uncommon, these patients' treating physicians should be aware of such possibility. Surgical removal of the NET is the first-line therapy and is potentially curable if there is no significant delay in the diagnosis.

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P139

Prevalence of undiagnosed Medullary Thyroid Carcinoma and Phaeochromocytoma in MEN2A syndrome revealed by cascade screening

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Mutations in the RET gene are responsible for Multiple Endocrine Neoplasia type 2A (MEN2A), characterised by Medullary Thyroid Carcinoma (MTC) and Pheochromocytoma (PCC). It is well recognised that there is a genotype-phenotype correlation regarding likelihood of endocrine tumour development. The American Thyroid Association (ATA) has published predictive grading to guide clinical management of patients with RET mutations.
Aim
In this study, we aim to assess the prevalence of MTC and PCC in asymptomatic patients, diagnosed with a RET mutation as a result of cascade screening of a proband relation.

Method
Review of electronic records, notes and clinical material collected from patients referred to NET (Neuro Endocrine Tumors) MDM and regional genetics referral centre over last 15 years. The database revealed 30 patients with confirmed MEN 2A, of which 20 were diagnosed after cascade genetic screening. Data from 18 patients was included in the study.
Results
There were 12 males, 6 females with mean age of 32.4 ± 22.5 years (mean ± S.D.). 8/18 asymptomatic patients (44.4%) had endocrine tumours diagnosed at or within 12 months of screening (mean age at MEN 2A diagnosis 41.3 ± 16.7 years). 100% (8/8) patients had histologically confirmed MTC, although serum calcitonin was elevated in only in 6/8 (range 16.9–3900 ng/l). 3 of these 8 patients (17%) also had PCC at diagnosis (with elevated catecholamines/ metanephrines), 2 bilateral and 1 unilateral (13 × 7 cm). In patients with tumour, the most frequent ATA Class was B (7 patients) followed by Class C (1 patient). The most common mutations were of codon C609Y and codon C620R in Exon 10 in 3 patients each, followed by C609R and C634R in 1 each. All 3 patients with synchronous PCC and MTC at presentation had ATA Class B mutations (C620R: 2 patients and C609Y) in Exon 10. In this cohort, mutations were found in Exon 10 in 88% and in Exon 11 in 12%.
Conclusion
Our study revealed the prevalence of previously undiagnosed tumours with cascade screening as 44% for MTC and 17% for PCC. This information is helpful in counselling during cascade screening. These findings emphasise that all patients with MTC should have RET mutation screening.

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P140

Achievement of therapeutic mitotane concentrations in management of advanced adrenocortical cancer: a single centre experience in 47 patients

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Introduction
Multi-modal therapy for adrenocortical carcinoma (ACC) includes surgery, therapy with the adrenolytic agent mitotane and systemic chemotherapy. Achievement of therapeutic mitotane concentrations (≥ 14 mg/l) has been related to improved outcomes.
Aim
To evaluate the effectiveness of a defined* high dose protocol mitotane therapy in patients with advanced ACC (stages III and IV).
Methods
Review of patients presenting to KCH with stage III or IV ACC and the mitotane concentration achieved through the Lysosafe monitoring service.
Results
$N = 57$ patients were referred and first diagnosed with ACC (2008-17) of whom 44 patients had stage III or IV disease at diagnosis and were managed actively with surgery and/or mitotane therapy. 40/44 patients underwent surgical resection of the primary tumour;11/22 patients with stage IV disease subsequently received systemic chemotherapy [10 patients received a combination of etoposide, doxorubicin and cisplatin (EDP) and 1 patient received a combination of carboplatin and etoposide]. 38/44 patients were initiated on mitotane therapy. The median overall survival of patients with stage IV disease was 25.3 months. The median survival for stage III has not been reached. An additional 9 patients had prior management, including surgery, elsewhere and were referred for mitotane initiation. A total of 47 patients were therefore included in the mitotane pharmacokinetic analysis. Six patients were excluded: 3 patients died shortly after mitotane initiation, 1 patient withdrew due to a severe reaction and 2 patients had not completed 12 weeks therapy at the time of submission. Of the remaining 41 patients, 33 commenced the 'high dose' protocol and the remainder the 'low dose' protocol. For patients on the high dose protocol, 25/33 (76%) reached a mitotane concentration ≥ 14 mg/l within 12 weeks of initiation of therapy, compared to 3 patients from the low dose protocol group ($P = 0.084$). In the high dose protocol group, 21 patients (84%) maintained therapeutic drug concentrations in ≥ 50% of the subsequent follow-up samples and 12 patients (48%) maintained therapeutic drug concentrations in ≥ 75% of subsequent samples.
Conclusion
The use of high dose protocol mitotane therapy is a successful strategy to achieve and maintain therapeutic drug concentrations when treating patients with advanced ACC (stages III and IV). In combination with an assertive surgical approach and optimal chemotherapy, this has resulted in outcomes that compare favourably (median OS 25.5 months in stage IV disease) with previously published series which describe a median OS < 12 months.
*Kerkhofs JCEM 2013

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Patients with metastatic bone disease and neuroendocrine neoplasms: the experience of a multi-center study

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Introduction
Neuroendocrine neoplasms (NENs) have variable biological behavior but the majority exhibits a slow progression. Metastatic bone disease (mBD) in NENs is relatively uncommon and not well described albeit associated with an increased mortality.
Methods
Seventy-four [37 males (50%), aged(± S.D.) 60.2 ± 19.3] patients with NENs and bone metastases were recruited from 4 centers.
Results
Seventy-three (98.6%) patients had sporadic disease while 1(1.4%) had MEN-1. The primary disease sites were: pancreas: 22(29.2%); small bowel: 18(24.3%); unknown origin: 12(16.2%); lung: 11(14.9%); sigmoid: 4(9.5%), thymus: 2(2.7%), breast: 1(1.4%) and caecum 1(1.4%). Four (5.4%) had functional syndrome, 2 ACTH-ectopic syndrome and 2 carcinoid syndrome. Thirty-four (46%) patients had synchronous diagnosis of NEN and mBD, while in the remaining the time to mBD since first diagnosis was 27.9 ± 56.7(0-383) months. Metastatic deposits were found as following: liver 48(64.9%), lymph nodes 24(32.4%), adrenal gland 4(5.4%), lymph nodes 11(14.9%), retroperitoneal and pelvic implantation 2(2.7%), mediastinum 2(2.7%), orbital brain 2(2.7%), brain 1(1.4%), parotid gland 1(1.4%), ovaries and uterus 1(1.4%), pancreas 1(1.4%). Sixteen (28.1%) patients had Ki-67 ≤ 2% (grade 1), 27(47.4%) 3-20% (grade 2), 25(15.8%) > 20% (grade 3) for gastro-intestinal NENs and for lung and thymus all 9(15.8%) had atypical NENs. The treatment for mBD included bisphosphonates in 40 (74%), peptide receptor radionuclide therapy (PRRT) 29(39.2%), denosumab 13(17.6%), and RT 13(17.6%). The imaging studies dentified mBD as following: 45/54(83.3%) bone scan, 21/35(60%) MRI, 36/67(53.7%) CT, 35/54(64.8%) octreoscan, 11/21(52.4%) PET-FDG and 28/30(93.3%) gallium-68 positron emission tomography (Ga-PET). The mBD therapy resulted in improvement in 6.3%, stable disease in 45.3%, and deterioration in 37.5% while 10.9% of patients passed away before the evaluation of treatment response. No difference was seen after treatment with an intensified bishphosphonate scheme (4 mg of zoledronic acid monthly for 2 consecutive years) versus a conventional scheme. Overall, 30(40.5%) patients succumbed because of their disease with an overall survival 67.1 ± 76(1-447) months since the NEN diagnosis.
Conclusion
The present multicentre registry of patients with NENs and mBD highlights the validity of Ga-PET for mBD identification and implies that there is no need of an intensified treatment at least for bisphosphonates despite the higher mortality rate of this subgroup of patients with NENs.

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Clinical features of 'dedifferentiation' in advanced pancreatic neuroendocrine neoplasms: the experience of two centers of excellence

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Introduction
Neuroendocrine neoplasms (NENs) exhibit significant heterogeneity in growth rates. Clinical and histopathological dedifferentiation has been documented but their clinical characteristics have not been described.
Aim of the study
The identification of clinical features of a series of pancreatic NENs (pNENs) that developed dedifferentiation during their course.
Methods
Fourteen patients (eight males) with mean age($\pm$S.D.): 54.8$\pm$12.4 years were recruited from two centers. Patients with documented disease progression were submitted to a new biopsy. Dedifferentiation was defined as histologically proven higher Ki-67 (%) able to increase the grade of neoplasm. Immunohistochemical analysis (IHC) for p53, β-catenin and E-cadherin were studied as markers of aggressive behavior.
Results
Twelve (85.7%) patients with a $>$10% change in Ki-67 had sporadic pNENs and 2 with $<$10% had pNEN in the context of MEN-1. At presentation, 1 (7.1%) patient had a NEN stage I, another stage III, 12(85.7%) had stage IV; 5 (35.7%) patients had a grade 1 NEN, 8 (57.1%) had a grade 2 NEN, and 1 (7.1%) had a low grade 3 (Ki-67:25%). After dedifferentiation 2 patients had low grade 2 (Ki-67$<$10%), 1 high grade 2, 3 (21.4%) had low grade 3(Ki-67$<$50%), and 8 (57.1%) had high grade 3 (Ki-67$\geq$50%); metastatic sites included, only liver:6, liver and bone:1, liver and lymph node:4, liver, lymph node, peritoneal implants:1. All patients had a positive octreoscan; 5 had functional syndrome (two gastrinoma, one carcinoid syndrome, one insulinoma, one VIPoma). The time of dedifferentiation, five patients were under molecular-targeted treatment (everolimus or sunitinib) with or without somatostatin analogs, four chemotherapy, three peptide receptor radionuclide therapy (PRRTs), one chemotherapy and PRRTs and one follow-up only. Eight lines of treatment were registered. At the last follow-up, 6 (42.9%) patients were alive with an overall survival 81.1$\pm$72.2 (9.46–263.3) months. The progression free-survival (PFS) for 1st line treatment was the only factor to predict time to dedifferentiation. No factor studied predicted mortality or the magnitude of Ki-67 increase. IHC for p53 was abnormal in 80% (4/5) cases all after dedifferentiation while β-catenin and E-cadherin had unaltered pattern of expression.
Conclusions
Dedifferentiation of NENs is associated with a more aggressive behavior and worse overall survival. More studies are needed to clarify if p53 may be used as immunohistochemical marker of dedifferentiation.

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Clinical features of a gastric neuroendocrine neoplasms type 1 series

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Background
The aim of the study was to assess the clinical features of gastric neuroendocrine neoplasms type 1 (GNEN1).
Methods
We have analyzed the clinical data of the first 73 patients with GNEN1 from our registry.
Results
The mean age($\pm$S.D.) of the patients (51 (68.9%) females) and the mean follow-up were 55$\pm$12.3 years and 28.8$\pm$42.2months, respectively. All patients had sporadic tumors and all were not functional. At diagnosis gastrin levels were 1086.4$\pm$946.7 pg/ml ($<$110). Anti-parietal cell antibodies (APCA) were positive in 91.1% (51) of the patients, autoimmune thyroid disease was found in 56.8%, and another autoimmune disease was reported in 21.9%. Median value of Ki-67 was 2 (interquantile range, IQR: 2, $<$1–20); 58.2% (39) patients had Ki-67$\leq$2% and 41.8% (28) had Ki-67$\leq$20% no neoplasm had Ki-67 $>$20%. The immunohistochemical analysis showed positivity for ghrelin in 3(4.1%), serotonin 2(2.7%), neuron specific enolase in 2, vasoactive intestinal peptide in 1 specimen and evidence of some ulceration (micro- or macro-) in 13 (17.8%) patients. Three (4.1%) patients had metastasis (two in liver and one in lymphnodes). Somatostatin receptor scintigraphy (SRS) was performed in 24 patients and was positive in 4 (16.7%). Regarding treatment, 16 patients received somatostatin analogues, 1 received everolimus, 12 (16.4%) patients were submitted in gastrectomy (total, partial or antrectomy). In the first year follow-up in 53.84%(21/39) GNEN-1 recurred [28.9% (6/21), Ki-67$>$2%], in the second year follow-up 56.3%(9/16) (12.5%(1/8), Ki-67$>$2%), in the fifth year follow-up 33.3%(4/12) (all Ki-67$\leq$2%), while following years all cases had Ki-67%$<$2% that 2 (one with 5% and the other 3%). No death was reported in the studied population.
Conclusion
Our study showed that despite the fact that the prevalence of grade 2 GNEN1 is higher than previously, GNEN1 remains a benign disease.

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Female Reproduction

P144

Female fertility in congenital adrenal hyperplasia

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Introduction
Congenital adrenal hyperplasia (CAH) is a genetic disease with autosomal recessive inheritance. The deficit in 21-hydroxylase (21-OH) is by far the most common enzyme deficiency CAH, since it represents 95% of the cases. Fertility in wome is found to be reduced due to hormonal, mechanical and psychological factors.
Patients and methods
It is about a descriptive and prospective study conducted in 15 patients collected in the endocrinology department of Sfax University hospital center. Fertility was evaluated by realising hormonal assessment of FSH, LH, testosterone, prolactin, estradiol and AMH. Pelvic ultrasound was also practiced in search of polycystic ovaries aspect.
Results
At the end of this report we concluded to a hypogonadotropic hypogonadism in a patient and a drop in the AMH hormone in four patients (33.3%). Pelvic ultrasound revealed micropolycystic ovaries in five patients. Referring to 2003 Rotterdam criteria, polycystic ovary syndrome was retained in six patients (40%). Five spontaneous pregnancies happened in three patients resulting in three abortions and the birth of two newborns with unambiguous female phenotype.
Conclusion
The prognosis of fertility in the CAH remains a priority for women in their fertile years. Genetic counseling in this case, is necessary.

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Neuroendocrinology

P145

Non-functional duodenal neuroendocrine carcinoma- a rare cause of diabetes mellitus

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Case history
We present a 40 year old female admitted with hyperglycaemia, polyuria, polydipsia and weight loss of 6 kg over a 1 month period. She had no night sweats or change in bowel habit. There was no personal or family history of malignancy or diabetes mellitus. She denied any alcohol, cigarette or illicit drug use. She took no prescription or OTC medication. On examination, she was jaundiced with pale mucous membranes. The rest of systemic examination was normal. Capillary glucose was 23.1 mmol/l.
Investigations
FBC, LFT, U and E, HbA1c, Urinary ACR, blood film, fasting gut hormone profile, CT- chest, abdomen and pelvis, duodenoscopy and biopsy, MRI liver, Octreotide scan, Endoscopic Ultrasound and biopsy, Screen for MEN 1 syndrome
Results and treatment
Hb – 64, Wcc – 8.4, platelet count – 346, lab glucose – 21.8 mmol/l, T -bili 48, Alp 687, Ast – 96, Alt – 117, Urea – 2.5, Cr – 52, Na – 136, k – 4.6, HbA1c – 79 mmol/mol, Blood film – iron deficiency anaemia, Urinary ACR – 5.4, pituitary profile, calcium and PTH normal
Fasting gut hormones
Vip – 4 (<30 pmol/l), pancreatic polypeptide – 12 (<3000 pmol/l), gastrin – 8 (<40 pmol/l), glucagon – 14 (0–50 pmol/l), Somatostatin – 174 (0–150 pmol/l), chromogranin A – 78 (0–60 pmol/l), chromogranin B – 49 (0–150 pmol/l). Duodenoscopy and biopsy- flat velvet like lesion in anterior wall of 2nd part of duodenum around ampulla. Biopsy – tubovillous adenoma with low grade dyplasia, CT chest, abdomen, pelvis – significant dilatation of intra and extra hepatic biliary tree including pancreatic duct. Periampullary 30 mm mass lesion projecting into lumen of duodenum. Enlarged nodes around superior mesenteric artery. Confirmed on MRI liver. EUS and biopsy mass in medial wall duodenum. Suspicious node over SMA. Fine needle biopsy of duodenal wall and lymph node in keeping with grade 1, well differentiated neuroendocrine tumour NM octreotide whole body scan and Spect CT- no uptake Treatment-BD mixed insulin, transfused to Hb>8 g/dl whipples pancreatico-duodenectomy R0 pT3 pN1 well differentiated neuroendocrine carcinoma arising in duodenum grade G1 (Ki 67: 0.5%) venous invasion present involvement of 4 of 17 lymph nodes.
Conclusions and points for discussion
Duodenal NET with main pancreatic duct obstruction can present with hyperglycaemia and cause diabetes. This is in the absence of gluconeogenic hormones such as somatostatin and glucagon. There was complete resolution of diabetes post Whipple's procedure and patient is now off insulin. Her last HBA1C was 31 mmol/mol.

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P146

Preliminary study of *POU1F1* (Pit1) gene expression in lactotroph and thyrotroph neuroendocrine tumours

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Introduction
The last World Health Organization (WHO) 2016 classification of Pituitary Tumours recommends the determination of transcription factors. During the last few years, silent variants of the main pituitary tumours (PTs) have been described. The mechanisms of silencing of these tumors are still unknown. *POU1F1* (Pit1) encodes a member of the POU family of transcription factors that has a relevant role in the differentiation, proliferation and survival of three pituitary cell types: somatotroph, lactotroph and thyrotroph lineage. It regulates the expression of GH, PRL and TSH-beta in the anterior pituitary gland.
Aim
To analyze the gene expression of *POU1F1* in a series of lactotroph and thyrotrophtumours, both functioning and silent, in order to observe if there are differences between the functioning and silent variants in both subtypes.
Material and methods
We selected 24 samples of PTs (seven functioning lactotropinomas (FLT), five silent lactotropinomas (SLT), three functioning thyrotropinomas (FTT) and nine silent thyrotropinomas (STT)) from our collection of 258 PTs. The tumours were previously molecularly identified on the basis of the expression of gene expression. Silent tumours were defined when the gene expression of PRL or TSHβ in the correspondent subtypes were similar to the respective functioning tumours, but without symptoms. The gene expression of *POU1F1* was performed using qRT-PCR with TaqMan probes. The data are expressed as the mean and S.D. of the Fold Change (FC). The ANOVA test was used to analyze differences between functioning and silent tumours in both subtypes.
Results
There were no significant differences in the expression of *POU1F1* between LT and TT subtypes in the overall series (2.87 ± 2.11 vs 2.00 ± 1.11, $P=0.266$) and between their respective silent or functioning tumours (1.39 ± 1.45 vs 1.91 ± 1.26, $P=0.797$; 3.94 ± 1.89 vs 2.27 ± 0.48, $P=0.267$). FLT but not FTT expressed more *POU1F1* than their silent variants (FLT vs SLT:3.94 ± 1.89 vs 1.39 ± 1.45, $P=0.036$); FTT vs STT (2.27 ± 0.48 vs 1.91 ± 1.26, $P=0.983$).
Conclusions
The lower expression of *POU1F1* in the silent variant of functioning lacto and thyrotropinomas could contribute to the silencing of these tumours. The absence of statistical significance in TT could be attributed to the short number of analyzed tumours.

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P147

Ectopic cushing's syndrome: Six cases description

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Introduction
Ectopic Cushing's syndrome (ECS) is due to ACTH secretion of no pituitary neuroendocrine tumors and represents around 5–10% of all cases of ACTH dependent Cushing's syndromes.
Methods
Six cases of ECS diagnosticated from 2008 to 2017 were studied. Patients' age ranges from 36 to 69 years (mean 53), four females and two males. Three had pancreatic tumors, two small cell lung carcinomas and one pheocromocytoma. At diagnosis, in 83% disease was disseminated. Hypercortisolism was diagnosed before neoplasic process in five cases. All patients presented rapid clinical evolution except for patient with pheocromocytoma. Weakness, hyperpigmentation, edema, hypertension and diabetes mellitus were the most important signs and symptoms. two patients presented severe psychotic disorders. Hypokaliemia was observed in five cases (mean potassium level 2.35 mEq/l) and metabolic alkalosis in 4. Bioquimical parameters were: cortisol 73 μg/dl (29.2–136.6), ACTH 561.1 pg/ml (46–1884), urinary cortisol 6596.9 μg/24 h (226–2,3247), nugent 60.5 μg/dl (26.9–135). All patients were treated to control the hypercortisolism, one with ketoconazole, two with metopirone, two with combination of ketoconazole and metopirone and one with mifepristone. No bilateral adrenalectomy were performed, only one adrenal embolectomy. Surgical removal of primary tumor was performed in two pancreatic tumors and pheocromocytoma, and four were treated with chemotherapy. Five patients died few months after diagnosis, pheocromocytoma is cured and one patient with lung carcinoma is under control but is suffering tumor progression.
Conclusions
Any neuroendocrine tumor may be associated with ECS. Survival depends on primary tumor histology, presence of metastases and severity of hypercortisolism.

This is why a multidisciplinary approach is required for the correct diagnostic and therapeutic management.

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P148

Metastatic meduller thyroid cancer patient with MEN 2B who developed acute leukemia

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Introduction
Multiple endocrine neoplasia type 2B (MEN 2B) is an aggressive disorder characterized by medullary thyroid cancer (MTC) and pheochromocytoma. Peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE is an effective new treatment for inoperable or metastatic neuroendocrine tumors (NETs). Hematologic problems, myelodysplastic syndrome or leukemia can be seen after alkylating agent and peptide receptor radionuclide therapy treatments. We present metastatic meduller thyroid cancer patient with MEN 2B who developed acute leukemia after treatment with 177 Lu-labeled peptide receptor radionuclide.
Case
28-year-old female was diagnosed with MEN 2B (thyroid medullary carcinoma, bilateral pheochromocytoma, and mucosal neurinoma) in 2015. Bilateral adrenalectomy and bilateral thyroidectomy with neck dissection was performed. The patients RET gen mutation was heterozygote positive. Liver biopsy for a liver mass showed metastasis of medullary thyroid carcinoma. F18-FDG-PET-CT revealed metastases in liver, lungs, and bone therefore she received alkylating chemotherapy of 6-cycles. ^{68}Ga-labeled somatostatin analogue PET/CT was revealed progression in metastatic lesions(somatostatin receptor positive) and increase in calcitonin levels after 12 months from the last cycle of chemotherapy. Six doses of Lu-177 DOTATATE was administered. After 9 months from the last dose of Lu-177 DOTATATE treatment progression in metastatic lesions and increase in calcitonin levels occurred and a new treatment was planned. However, her blood count revealed pancytopenia and bone marrow aspiration revealed promyelocytic cells. Genetic tests and flow cytometry analysis was consistent with acute promyelocytic leukemia (AML M3). Chemotherapy was planned for leukemia after ATRA treatment.
Conclusion
A decrease in bone marrow reserve, more rarely myelodysplastic syndrome (MDS) and leukemia may occur after PRRT. As with our patient, the risk of MDS increases when alkylating agents and PRRT are used together. Researchers state that acute leukemia (AL) occurred after a median follow-up of 55 months after first therapy (range 32–125 months). In our patient, acute promyelocytic leukemia occurred 18 months after the first PRRT treatment.

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P149

Diagnostic difficulties, management and treatment in neuroendocrine tumors

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Introduction
Diagnosis of NETs (neuroendocrine tumors) is based on clinical manifestations, peptide and amine secretion, specialized radiological and nuclear imaging, secured by detailed histology and immunohistochemistry, which should be obtained whenever possible. Biomarkers are still the mainstay in the diagnosis and follow-up of patients with NETs.
Case report
We present the case of a 36-year-old patient with no significant pathological personal history, diagnosticated in 2015 with amesenteric tumor/jejunal GIST (gastrointestinal stromal tumor) and lymphadenopathies adjacent to the II–III jejunal branches. Surgery was performed, with good postoperative evolution. The histopathological exam shows malignant proliferation with solid and cordial architecture, areas of intratumoral necrosis and multiple images of vascular invasion; five lymph nodes present tumor metastasis. Immunohistochemistry assays decelerate synaptophysin, CD99 positive in most tumor cells, rare positive NSE and negative cromogranin; Ki67 positive in 10% of tumor cells. The final diagnosis was neuroendocrine tumor (NET G2). The patient met the criteria for inclusion in somatostatin analog therapy, but it was schedule on demand. Between 2016 and October 2017: chromogranin A, serotonin and 5-hydroxy indolacetate were negative, no recidives on CT scan. In November 2017, the patient was admitted for weight loss, abdominal pain, nausea. Biologically, the carcinoembryonic antigen was over the upper limit, with anemia and important inflammatory syndrome. CT scan describes adenopathies in the left flank, with central necrosis and tendency to confluence, and three new hepatic nodular lesions, suspected of secondary dissemination. Surgically reintervention with the excision of the hepatic formations and the lymph node was performed; immunohistochemistry detects synaptophysin, CD56, NSE positive in the hepatic lesions with negative cromogranin; negative synaptophysin, cromogranin and CD99, with positive CD56, NSE in lymph nodes and Ki67 20% in both sites. SSTR2 and SSTR5 receptors were also positive. A Tektrotyd (Technetium 99mTc-HYNIC-Tyr3-Octreotide) scan confirmed the presence of the radiopharmaceutical pathological capture in the hepatic VI and III segment, grade Krenning 3, with a limited tumor dissemination score. Considering the aggressive progression of the disease, the dissemination rate, the Ki67 increase from 10% to 20% in a short time, we opt for somatostatin therapy and PRRT treatment initiation, the patient fulfilling the inclusion criteria (Krenning score $>$ 2).
Conclusions
The diagnosis delay, the trap of negative usual neuroendocrine markers and the refusing of the specific treatment, lead to unfavorable disease progression, aggressive growth of Ki67, which together can lead to therapeutic failure.
Keyword: neuroendocrine tumor, negative markers, Ki67

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P150

Through five hospitals and 800 km, a long way from emergency department to insulinoma operation

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Introduction
Urgent conditions, as first symptom of endocrine disease, are rather rare in a hospital emergency department. Emergency medicine doctors work in difficult conditions, often under time pressure, they must also be guided by the likelihood of linking symptoms to the disease. Unfortunately, this makes it difficult to diagnose rare diseases. Therefore, without criticising doctors of other specialties, we would like to present our patient's long journey from the emergency department to an effective operation.
Case
A 33-year-old woman was brought to a hospital emergency department in a district hospital due to an acute psychotic episode. In the absence of a response to the treatment, she was transported to a psychiatric hospital, where initially her condition improved slightly. Unfortunately, in the further course convulsions appeared and with suspected state of epilepsy she was transported to the neurology department, where despite intensive pharmacotherapy and mechanical ventilation her condition did not improve. A dramatic improvement occurred when the consultant internist ordered blood glucose control (29 mg/dl) and subsequently glucose infusion. In the endocrinology ward during the hunger test,

hypoglycaemia was found, but with not very high insulin levels, which did not allow unambiguous diagnosis of insulinoma. In the gastrology clinic, extended imaging diagnostics with MRI and an EUS were performed combined with a biopsy of the 29×15 mm "nodula" adjacent to the head of the pancreas. However, the result of the biopsy did not confirm the diagnosis of insulinoma. Meanwhile, the patient 'disappeared" from observations of endocrinologists from the first hospital, but after 2 months "was found" in a clinic of endocrinology 400 km away. In this time the values of insulin and C peptide during spontaneous hypoglycaemia met the criteria for insulinoma diagnosis, which was also confirmed by the histopathological examination after surgical removal of the nodule. The patient in good general condition remains under the control of the endocrinology clinic. From the psychotic episode in the hospital emergency department 105 days have passed to the operation and from the first discrete symptoms 13 months.

Conclusion

Diagnosis of insulinoma in department of emergency is practically impossible, However, adherence to the principle of blood glucose testing in each patient in department of emergency probably slightly shortens the path to proper diagnosis and effective treatment.

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P151

A rare association of neuroendocrine tumors

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Background

The occurrence of multiple endocrine tumors in the same patient is not always typical and cannot always be classified into a multiple endocrine neoplasia (MEN) type, McCune-Albright syndrome or the Carney complex. Schwannomas are mesenchymal tumors that originate from Schwann cells of peripheral nerve fibers that can associate in some syndromes. 90% cases are benign, involving usually the head, neck and extremities. They are rare in the retroperitoneal region (1–3%).

Case report

We report the case of a 49-year-old female patient, Caucasian, non-smoker, who was previously diagnosed (in 2008) with ACTH-independent Cushing's syndrome due to a cortisol secreting adenoma of the right adrenal gland (30/25mm). She had undergone right adrenalectomy (histopathologic exam and immunohistochemistry confirmed the diagnosis) and received one year of hydrocortisone replacement. In 2016, due to recurrence of malignant hypertension, the CT scan revealed in the right adrenal lodge a multilobulated, well-defined, heterogeneous mass, measuring 50/23 mm, that was compressing the superior vena cava and also a small adenoma (0.7/1 cm) on the left adrenal gland and left renal cysts. The patient had only a mild discomfort in the right flank. Adrenal function evaluation results were normal, excluding recurrent Cushing's syndrome, pheocromocytoma or primary aldosteronism. Pituitary function was also normal. Further testing revealed hypercalcemia (11.3 mg/dl), elevated parathormone level (103 pg/ml), insufficient level of 25-OH-Vitamin D (17.02 ng/ml), normal renal function (CKD-EPI eGFR = 97.02 ml/min per 1.73 m^2 and normal calcitonin (excluding medullary thyroid cancer). The anterior cervical ultrasonography showed a hypo-echogenic nodule (1.23/1.6 cm), suggestive for parathyroid adenoma. The patient was then referred to surgical service in order to remove the retroperitoneal mass of unknown origin by laparoscopic approach. The histopathologic and immunohistochemistry (S100, SYN, Melan A and VIM diffusely positive) exams indicated an ancient schwannoma. The patient is scheduled for sestamibi parathyroid scintigraphy. Further on, depending on the scintigraphy result, the patient will be advised to undergo parathyroidectomy and will be periodically screened for other occurrences.

Conclusion

The association between ACTH-independent Cushing's, schwannoma finding in the same adrenal lodge after adrenalectomy and recently discovered primary hyperparathyroidism, is very rare and it may be genetically determined in the context of MEN or other syndromes, but can also be sporadic. Also, retroperitoneal ancient schwannomas are very rare, and the occurrence of it after adrenalectomy has not yet been reported, so we cannot know for sure if there is a connection with these endocrine conditions.

Keyword: Cushing's syndrome, hyperparathyroidism, ancient schwannoma

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P152

Head and neck paragangliomas: genetic mutation and location of the tumors

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Introduction

Tumors derived from the paraganglionic system are rare. 90% of them are located on the adrenal gland, and the remaining 10% are extra-adrenal. Within this last group, 85% are located in the abdomen, 12% in the thorax, and 3% in the head and neck region (HNPG). Its proximity to important structures represents a great difficulty for resection. This makes it necessary to refer these patients to reference centers with multidisciplinary teams and specific surgical training.

Objectives

To determine whether there is a correlation between the genetic mutation of the head and neck paragangliomas, their location and the presence of metastasis.

Methods

Retrospective study. Inclusion criteria: patients with head and neck paragangliomas (HNPG) treated in our hospital between the years 2000 and 2016. In total, 97 patients were included, 65 women (66%) and 32 men (33%), with an age range of 14–84 years (mean age: 49 years). All of them were surgically removed. The SDHB, C and D genes were studied.

Results

Ninety-eight percent of the tumors were nonfunctional (normal metanephrines in urine after 24 h). Out of the 97 patients, 24 (23%) showed genetic mutations. Within this group, 9 patients had the *SDHB* mutation (41%); 8 patients had the *SDHC* mutation (37%); and 5 patients had the *SDHD* mutation (20%). There was no correlation between the genetic mutation and the location of the tumor. In the patients with *SDHB* mutation, 11% had a metastasis on diagnosis, compared with 3% in the group with sporadic tumors. Vagal HNPG represented 11% (10 patients) and had a higher malignacy rate: 15% of the cases.

Conclusions

In the HNPC in our series, the most frequently found mutation was *SDHB*, which was not associated with the location and which showed shorter survival in cases with metastasis.

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P153

Bilateral neck paragangliomas in a patient with a family history and chronic hypoxemia

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Introduction

Tumors derived from the extra-adrenal paraganglionic system are rare (incidence: 0.8/100,000 people/year). In this group, 85% are located in the abdomen, 12% in the thorax, and 3% in the head and neck region (HNPC).

Case report

A 46-year-old man, ex-smoker, with a personal history of arterial hypertension, multifactorial secondary polycythemia (obesity, OSA syndrome, hypertrophic cardiomyopathy). Family history: one brother with paraganglioma. The patient presented symptoms of asthenia and neck pain.

Complementary tests

Laboratory: Hb: 20.5 g/dl; Hct: 59.6%; Ca: 12.7 mg/dl; PTH: 353 pg/ml; Calc. urine: 398 mg/24 h; Normetanephrines in urine: 599 mcg/24 h.

Neck CT scan: Bilateral laterocervical masses on both carotid bifurcation. The mass on the right side is 2.4x1.7x3.9 cm and the mass on the left side is 6.5x3.2x7.5 cm.
Scintigraphy (octreotide): laterocervical masses which express somatostatin receptors. The lesion on the right side shows more metabolic activity.
Diagnosis: Bilateral HNPG, clinically silent, which does not extend beyond the cervical region.
Evolution: The patient was operated to treat the HNPG.
Genetic study: Exons 1 to 8 of the SDHB gene, exons 1 to 6 of gene SDHC and exons 1 to 4 of gene SDHD were studied with PCR and BigDye sequencing. No pathogenic mutations or variants of unknown origin were found in the regions analyzed.
Discussion
In this patient is probably a familial paraganglioma syndrome (bilateralism and one brother with a similar condition). The genetic study performed did not come to any final conclusion on the origin of the disease (it did not analyze the SDHAF2 gene, whose mutation is typical in HNPG). The pathogenesis of HNPG is not completely known. The mutation of some specific genes (HID, SDH and VHL) create a similar effect to the stimulation of paraganglionic cells due to chronic hypoxia. Mutations of VHL and SDH are related to these routes of cell hypoxia, and the tumors present associated angiogenesis and a decrease of oxidative metabolism. It is important to mention that HNPG lack histological or molecular markers for malignancy. Up to 50% of all malignant HNPG can be initially classified as benign. Currently, the only clinical predictors for the appearance of metastasis are the presence of the SDHB mutation and a tumor size over 5 cm. Our patient meets the second condition, and therefore will be subject to strict monitoring.

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P154

The first experience of using of ultrasound with multimodal imaging technology for the diagnosis of pancreatic insulinoma

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Introduction
Topical diagnosis of insulinoma is an actual problem due to the low detection rate of tumors (about 75%) and conflicting data about its localization in pancreas (more than 50%) when using different imaging techniques. This is partly due to the subjectivity of visualizing diagnosis specialists when describing the location of tumor. We assumed that multimodal imaging Fusion will improve the accuracy of topical diagnosis of insulinoma.
Aim
To determine the feasibility of Fusion technology for localization of insulinoma.
Materials and methods
We include 12 patients with laboratory confirmed hypoglycemic syndrome and autonomous insulin secretion aged 31-65 years. All patients underwent standard initial imaging examination for localization of insulinomas – computer tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US). In addition, we used the Smart Fusion (S-Fusion) intelligent program for synchronization real-time ultrasonography images and CT images, as well as MRI images. We created magnetic field next to the US machine and mounted magnetic sensors at the US transducer. Then we loaded data of CT (or MRI) and displayed image with tumor on the screen of US machine. The same section was obtained using the US transducer. Then we established anatomical landmarks on CT (MRI) and US images and synchronized them. In accordance with data obtained by combining the images we made topical diagnosis in all patients and then performed surgical treatment of insulinoma.
Results
There was a discrepancy in topical diagnosis, according to the standard initial imaging examination, in 5 patients (42%). The intelligent program S-Fusion helped us to clarify the tumor localization in these patients. This study also allowed to obtain more accurate information on the location of tumor (including in relation to vessels) in those patients in whom topical diagnosis was not doubt ($n=7$). The duration of ultrasound with the application of S-Fusion technology increased by only 5 minutes, and the cost was not changed. Intraoperative revision in all patients (100%) confirmed the presence of tumor of pancreas in accordance with the established topical diagnosis: in the head ($n=3$; 25%), body ($n=3$; 25%), tail ($n=6$; 50%). Microscopic examination confirmed the immunomorphological characteristics of insulin-producing tumors in all patients. In the postoperative period none of the patients had hypoglycemia.
Conclusions
Fusion technology eliminates the subjectivity of visualizing diagnosis specialists and provides more accurate information on the location of tumor. Advantages of this method are: non-invasiveness, absence of ionizing radiation, low cost and low duration of the study.

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Obesity

P155

Body composition and concentration of 25-OH vitamin D as metabolic syndrome indicators in patients with non-functioning adrenal incidentalomas

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Abstract
Up to 96% of changes detected in adrenal glands are non-functioning adrenal incidentalomas. Adrenal masses are associated with increased risk of metabolic syndrome (MS). Studies demonstrate that new anthropometric parameters can be useful indicators of disturbances in glucose and lipid metabolism in various diseases. The purpose of the study was to determine antropometric parameters and its relationship with MS factors according to the criteria of the International Diabetes Federation among patients with non-functioning adrenal incidentalomas. 120 patients hospitalized in Endocrinology City Hospital in Piekary in 2013-2017 with non-functioning adrenal incidentalomas were included to the study. Exclusion criteria were adenomas producting hormones, vitamin D supplementation, liver or kidneys failure. Biochemical parameters were obtained during routinely performed tests in the hospital and taken from the patient's medical record. Anthropometric parameters were measured in the morning. The results were used to calculate the anthropometric indicators (BMI, BAI, VAI, WHR, WHtR). The data were statistically analyzed by STATISTICA 12. $\alpha=0.05$. The average BMI was 29.5 ± 5.3 kg/m^2, WHR(women) 0.9 ± 0.2, WHR(men) 1.0 ± 0.1, WHtR 0.6 ± 0.1, BAI (women) 35.1 ± 6.2, BAI(men) $26.1\pm3.0\%$, VAI 2.1 ± 0.3. The average systolic pressure was 142 ± 18 mmHg, diastolic pressure 83.2 ± 9.5 mmHg. The mean concentration of $25(OH)D_3$ was 18.6 ± 7.7 ng/dl, total cholesterol (TC) 205.7 ± 44.9 mg/dl, HDL cholesterol(women) 66.2 ± 20.6 mg/dl, HDL cholesterol(men) 49.8 ± 16.7 mg/dl, LDL cholesterol 116.3 ± 40.3 mg/dl, triglycerides (TG) 135.9 ± 75 mg/dl, fasting glucose 112.3 ± 33.5 mg/dl, HBA1C% 6.3 ± 0.9. Possitive correlation ($p\leq0.05$) was observed between VAI and TC ($r=0.06$), VAI and LDL cholesterol ($r=0.34$), VAI and TG ($r=0.83$), WHR and TG ($r=0.08$), WHtR and TG ($r=0.04$). Systolic pressure was statistically higher ($p\leq0.05$) in patients with higher BMI ($r=0.11$), BAI ($r=0.06$), WHR ($r=0.09$;), WHtR ($r=0.14$). Fasting glucose correlated possitively ($P\leq0.05$) with BAI ($r=0.05$), BMI ($r=0.11$), VAI ($r=0.03$), WHR ($r=0.13$), WHtR ($r=0.16$), HBA1C% ($p\leq0.05$). Patients with higher $25(OH)D_3$ concentration had statistically lower HBA1C%, TC and LDL cholesterol ($p\leq0.05$). There were negative correlations ($p\leq0.05$) between HDL cholesterol and VAI, WHR, WHtR. Low $25(OH)D_3$ concentration may indicate lipid disorders in patients with non-functioning adrenal incidentalomas. BMI, BAI, VAI, WHR and WHtR are good inditators of metabolic syndrome in studied group of patients with non-functioning adrenal adenomas.

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Paediatric endocrinology

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Pediatric adrenal insufficiency: experience from a Tertiary Hospital Center

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Introduction
Adrenal insufficiency is a life-threatening disease caused by primary adrenal failure or secondary adrenal failure due to an impairment of hypothalamic-pituitary axis that affects adrenal cortisol synthesis. It is characterized by deficient production of glucocorticoids and may be associated with mineralocorticoid and androgens deficiency. Prompt diagnosis and management are essential and may even be life-saving.
Methods
We retrospectively collected and analysed clinical, laboratorial and radiological data from patients with adrenal insufficiency observed over a period of 34 years (January 1984–December 2017) in a Pediatric Endocrinology Department of a Tertiary Care Hospital.
Results
Seventy patients with adrenal insufficiency were identified:41 with primary adrenal insufficiency and 29 with central adrenal insufficiency. Primary adrenal insufficiency patients were mainly males (56%), with a mean age at diagnosis of 2 ± 4 years, followed for about 11 ± 6 years. Thirty-five patients (85%) had classic adrenal congenital hyperplasia, mainly due to 21-hydroxilase deficiency ($n = 33$), 3 patients had Addison disease, 1 had X-linked adrenoleukodystrophy, 1 had Pearson disease and 1 had bilateral adrenal haemorrhage. At the presentation, 73% of the patients had hyponatremia and more than half had mucocutaneous hyperpigmentation, asthenia, anorexia, weight loss, nauseas and vomiting; 46% presented with genital ambiguity.Mean ACTH level at diagnosis was 631 ± 449 pg/mL (reference range < 46.0) and mean cortisol level was 7 ± 5 µg/dL (reference range 5.0-25.0). All the patients were treated with hydrocortisone (mean dose 9 ± 5 mg/day) and 90% were also on fludrocortisone (mean dose 60 ± 20 µg/day). During the follow-up, one patient died for unknown causes. Regarding patients with central adrenal insufficiency, the majority were females (52%), with a mean age at diagnosis of 6 ± 5 years, followed for 9 ± 6years. Craniopharyngeoma was present in 31% of the patients,pituitary hypoplasia in 24% and 10% had a hypothalamic tumour. Besides corticotropin, the most common hormone insufficiencies were thyrotropin (93%), growth hormone (63%) and antidiuretic hormone (52%) deficiencies. The most frequent presenting clinical features were hypoglycemia (35%), nausea and vomiting (28%) and infectious diseases (28%) .93% of the patients were treated with hydrocortisone (mean dose 9 ± 8 mg/day). During the follow-up, 2 patients died due to cardiorespiratory complications.
Conclusions
Despite medical advances, the diagnosis and management of adrenal insufficiency remains a challenge, particularly in the paediatric population owing to their special characteristics. Raising awareness and knowledge in medical teams and population about adrenal insufficiency is of crucial importance to improve clinical outcomes and to reduce disease morbidity and mortality.

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Pituitary - Basic

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MicroRNA profile after octreotide treatment in neuroendocrine tumor cell line

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Abstract
Somatostatin analogs (SSAs) constitute first-line treatment for patients with neuroendocrine tumors. Somatostatin receptors (SSTRs) are the most common therapeutic, radiotherapeutic, and imaging targets of SSAs. Some G-protein-coupled receptors, including SSTRs, regulate their responsiveness to continuous drug exposure with different degrees of receptor internalization. Thus, SSTR internalization seems to play an important role in predicting the response to SSAs in patients with neuroendocrine tumors. The present study aimed to regulate SSTR internalization via miRNA profiling after SSA (octreotide) treatment in the rat pancreatic beta cell line INS-1. INS-1 cells were treated with octreotide at various incubation times (0–60 min) to confirm SSTR internalization via immunofluorescence staining. Internalization of SSTR2 in INS-1 cells was induced after 5 min of SSA treatment. Hence, we analyzed the changes in microRNA expression between 0 and 5 min after octreotide treatment. Using a greater than two-fold change in cut-off for miRNA expression, 49 probe sets were up-regulated at 5 min versus at 0 min of incubation, and 75 were down-regulated. Interestingly, miRNA involved in ubiquitination, such as rno-miR-504, rno-miR-99a-5p, and rno-miR-466b-3 were up-regulated. In conclusion, we identified miRNAs responsible for SSTR2 internalization. To modulate SSTR internalization by miRNA in tumor cells of a patient, treatment with SSAs would be clinically relevant, as this could improve the response to therapy or for tumor detection.

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Gender differences in delays to diagnosis of acromegaly: data from the Swedish National Patient Register

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Acromegaly is a complex disease with an insidious onset and diagnosis can be delayed. The aim of the study was to investigate the diagnostic delay (DD), for patients with acromegaly due to a pituitary tumour in Sweden. Data were obtained from the Swedish National Patient Register. Patients diagnosed between January 1, 2011 and December 31, 2013 in Sweden were included ($n = 135$, 69 men, 66 women). For these patients, the occurrence of pre-defined relevant comorbidities was assessed from 1987 and onwards. DD was defined as the time between the first diagnosis (outpatient or inpatient visit) of a relevant comorbidity and the date of acromegaly diagnosis. The median (95% CI of the median) overall DD for all patients included in the analysis was 52.4 (33.4–74.3) months. The median (95% CI of the median) DD for patients diagnosed during 2011 was 57.6 (27.4–80.5) months while corresponding numbers for 2012 and 2013 was 49.3 (13.6–74.3) and 47.7 (4.2–86.8) months, respectively. During the entire study period, there were 39 patients (29%) diagnosed within 6 months while 21 patients (16%) had a DD of more than 120 months. Patients with a first symptom diagnosis categorized as hypertension had a median (95% CI of the median) DD of 17.8 (2.6–120.9) months while corresponding numbers for patients with a first symptom diagnosis categorized as a cardiac diagnosis were 108.8 (1.6–150.8) months. The median (95% CI of the median) DD for men was 21.7 (4.2–53.3) months while it was 76.7 (55.0–89.2) months for women ($P = 0.0182$ using Log rank test). Hazard ratio (95% CI) with women as reference category was 1.50 (1.06–2.11). This analysis focused on a small population, but the reported DD was in line with previous published data. A limitation of this analysis is that data on primary care visits are not included in the registry; therefore, time between first primary care visit and diagnosis of a relevant comorbidity in secondary care is not captured in the DD calculated. During the short time frame of this study no changes in the DD for patients diagnosed during the different years can be detected. There are patients with very long DD, approaching the total follow-up time. This underlines previous findings that acromegaly has an insidious onset and that diagnosis can be complex. In this study, men were diagnosed 3.5 fold faster than women, indicating that women are not correctly diagnosed to the same extent as men.

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Direct costs after diagnosis of acromegaly: Data from Swedish nationwide registries

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Acromegaly and comorbidities incur large costs in the Swedish health care system. The aim of the study was to describe direct costs since time of diagnosis, for patients with acromegaly due to a pituitary tumour in Sweden. Data were obtained via linkage of nationwide registers. Patients diagnosed between 1 July 2005 and 31 December 2007 in Sweden and with a follow-up of at least 6 years were included ($n=105$). Direct costs due to use of health care resources and pharmacological treatments (somatostatin analogues [SSA], growth hormone receptor antagonists [GHRA], and dopamine agonists [DA]) were assessed. The mean total direct costs per patient were highest for year 1 after diagnosis (€18 108 [95%CI 15 952–20 265]) with surgical interventions being the main contributor (54%). For subsequent years, the mean (95%CI) costs ranged from a maximum of €8,770 (6733–10 807) (year 2) to a minimum of €6686 (4943–8429) (year 4), with acromegaly drug costs as the largest part. The share of direct costs due to acromegaly amounted to 95% (remaining 5% due to comorbidities) for the first year after diagnosis and fell to 86% (comorbidities 14%) during year 6. SSAs (lanreotide and octreotide) were the main contributors to drug costs (>86% throughout the study period). Costs for drugs for the treatment of acromegaly increased every year and rose from 15% during year 1 to 77% for year 6 with GHRA (47%), lanreotide (44%), and octreotide (9%) costs as contributors. DA costs decreased over time but were overall negligible. Over the follow-up period, the number of patients treated with lanreotide rose from 12 (11%) to 20 (19%) patients while corresponding numbers for octreotide fell from 26 (25%) to 13 (12%) patients. During year 1 and 2, no patients were treated with GHRA but this increased to eight (8%) patients during year 6. When the mean direct costs per patient using each drug were analysed, lanreotide costs increased 31% from year 1 to year 6. The corresponding increase for octreotide was 135% while the increase from year 3 to 6 for GHRA (pegvisomant) was 186%. Real world evidence from national registers allows detailed monitoring of changes in direct costs after diagnosis of acromegaly. Surgical interventions are a main contributor (54%) to the total direct costs during the first year after diagnosis, but pharmaceutical treatments become more important over time with SSA and, to some extent, GHRA as the main contributors.

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Steroid metabolism + action

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Urinary steroid profile in patients with primary adrenal insufficiency under conventional glucocorticoid replacement: a case control study

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Introduction
Primary adrenal insufficiency (PAI) leads to a drastically reduced production of steroids from the adrenal cortex, but a few patients may keep some residual adrenal steroid secretion that may simplify replacement therapy and prevent adrenal crisis. Irrespectively, the conventional glucocorticoid (GC) replacement therapy, using thrice-daily oral hydrocortisone, does not restore the patients' physiological cortisol profile.
Objective
The primary objective was to study enzyme activity related to GC action, synthesis and degradation in patients with PAI and GC replacement by assessing urinary steroid profile. The secondary aim was to analyze if any residual adrenal function can be detected in patients with long-standing PAI.
Methods
Case-control study comparing patients with PAI >6 months after diagnosis, under stable thrice-daily hydrocortisone replacement (20-40mgs/day) with healthy controls. Urinary steroid profile was measured using gas chromatography/mass spectrometry. Activity of enzymes involved in synthesis and metabolism of steroid hormones was evaluated by calculation of ratios (substrates/products).
Results
Fifty PAI patients (22 females, mean age 47 years (range 19-71)) were compared with 124 healthy controls (73 females, mean age 48 years (range 20-81). Urinary cortisol (F) ($P<0.001$) and cortisone (E) ($P<0.001$) excretion were higher in patients compared to controls. In contrast, urinary metabolites of F (5α-THF and 11β-OH-etiocholanolone) and E (THE, 11-oxo-etiocholanolone) were similar in patients and controls. The urinary THF+5αTHF/THE ratio reflecting 11βHSD1 activity and the urinary F/E ratio reflecting 11βHSD2 activity was higher in patients than in controls ($P<0.001$ and $P<0.01$ respectively). The F/5αTHF ($P<0.001$), THB/αTHB ($P<0.001$) and androstenedione/etiocholanolone ($P=0.023$) ratios were higher in patients suggesting a lower 5α-reductase activity. Similarly, ratios evaluating 5β-reductase, 20αHSD and 20βHSD indicated a lower activity in patients. Androgens, mineralocorticoids and their precursors as well as the GC precursors were drastically decreased in patients, although residual secretion of one or more steroids was detected in 9 patients.
Conclusion
The urinary steroid metabolome showed that activity of important enzymes involved in the modulation of corticosteroid action and metabolism was markedly abnormal in PAI patients treated with conventional hydrocortisone therapy. This results in an abnormal cortisol metabolite profile that may contribute to adverse metabolic effects. Production of androgens, mineralocorticoids and GCs is markedly reduced in PAI patients, although 18% of them exhibited residual steroid secretion.

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Steroid profile using gas chromatography tandem mass spectrometry (GC-MS/MS) in search for a steroid which correlates most with subclinical hypercortisolism

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Introduction
Gas chromatography tandem mass spectrometry (GC-MS/MS) quantitatively detects a large number of steroids at one time in a single serum sample. Most studies of subclinical hypercortisolism in adrenal incidentalomas have focused on detection of a few steroids like cortisol, DHEA/S, androstenedione, testosterone. We used GC-MS/MS to quantify 91 steroids in patients with adrenal incidentalomas to search for the most reliable marker of subclinical hypercortisolism.
Methods
Steroid profiles consisting of 91 steroids measured by GC-MS/MS from sera of 54 patients with unilateral ($n=29$) and bilateral ($n=25$) adrenal incidentalomas were compared. Suspected subclinical hypercortisolism was defined as cortisol >50 nmol/l (1.8 μg/dl) in 1 mg overnight dexamethasone (DXM) test. Sensitivity and specificity was calculated for urinary free cortisol >208 nmol/24 h, ACTH< 10 ng/l (2.2 pmol/l), midnight serum cortisol >149 nmol/l as sole criterion. Logistic regression and ROC curves were used to select steroids that best reflect non suppressibility in 1 mg dexamethasone test and ROC curves with sensitivity and specificity were calculated.

Results
Out of 54 patients 13 had suppressed cortisol in 1 mg DXM test under 50 nmol/l. Remaining 41 (21 unilat., 20 bilat.) had post DXM cortisol ranging from 51 to 381 nmol/l. UFC > 208 nmol/24 h showed 34% sensitivity and 76% specificity. ACTH < 10 ng/l had 17% sensitivity and 100% specificity. Midnight serum cortisol >149 nmol/l had 60% sensitivity and 84% specificity. DHEAS had sensitivity 71% and 85% specificity with cut off value =876 nmol/l, AUC= 0,800 and Z-score=3.07. Androsterone sulphate showed sensitivity 76% and specificity 69% with cut off value=539 nmol/l, AUC=0.780 and z-score=3.33. Androstenediol had 78% sensitivity 77% specificity with cut off value= 0.69 nmol/l, AUC 0,740, z-score=2.46. Other measured steroids had lower predictive values.
Conclusions
Non-suppressibility in dexamethasone test correlates with the suppression of DHEAS in most cases. Other steroids like androsterone sulphate, androstenediol and other show similar sensitivity and specificity but are difficult to measure in routine conditions. Diagnosis of subclinical hypercortisolism needs to be evaluated by a combination of parameters, which cannot be replaced by a sole criterion.

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Thyroid (non cancer)

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Clinical aspects of the schmidt's syndrome: a 14 years retrospective monocentric study

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Introduction
Schmidt's syndrome also known as autoimmune polyglandular syndrome type 2 (APS type 2) is a rare endocrine disorder defined by the combined occurrence of Addison disease with autoimmune thyroid disease. The rarity of the condition and the atypical presentation of adrenal insufficiency and hypothyroidism often lead to misdiagnosis with life-threatening consequences for the patient. In this study we report an exhaustive monocentric analysis of 22 patients diagnosed with a Schmidt's Syndrome.
Patients and methods
We carried out a retrospective study of all the patients diagnosed of a Schmidt syndrome or APS type 2 in the Department of Endocrinology and Diabetology of University Hospital Farhat Hached of Sousse, over a period from 1999 to 2013. Adrenal insufficiency was diagnosed with a basal cortisol level<40 ng/ml or peak <180 ng/ml after Synacthen. Autoimmune Hypothyroidism was diagnosed with a T4 <7 pg/ml and TSH >10 mUI/l associated with the positivity of anti-Peroxydase antibodies. We analyzed clinical and biological aspects of these patients with SPSS ver. 23.0 software.
Results
We reported 22 cases, with a mean age of 31.77±11.26 years old, with 36.3% between 20 and 39 years old ($P=0.02$) and a predominance for female sex with a sex ratio=0.22 ($P<10^{-3}$). The mean age of discovery of Addison's disease was 32.5±9.2 with extremes ranging from 12 to 58 years. According to the age of discovery compared to hypothyroidism, Addison disease was diagnosed significantly before the diagnosis of Hashimoto's disease in 59% ($P=0.03$), concomitant in 27.2% and posterior in 13.6%. Clinical symptoms made of melanodermia and hypoglycaemia suggested the diagnosis in 47% of all patients. An acute adrenal insufficiency was triggered by the hormonal thyroxin substitution in one case. Other autoimmune diseases were found in 27.2%, as a celiac disease (8%), type 1 diabetes (8%), Biermer anemia (7%) and autoimmune ovaritis in 4.2%.
Conclusion
Schmidt's Syndrome is more likely to be associated with the female sex and young age. In our study, Hashimoto's hypothyroidism was the first autoimmune disease discovered. The presence of at least one component of the APS type 2 must lead to the autoimmune screening of the other diseases. This screening could avoid the triggering of an adrenal insufficiency in thyroid hormonal substitution.

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Thyroid cancer

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Sentinel lymph node biopsy of jugulo-carotid regions in medullary thyroid microcarcinomas after methylene blue dye mapping – A single institution experience

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Introduction
Management of lymph nodes (LN) in medullary thyroid carcinoma (MTC) is an ongoing debate. Unpredictable behavior of MTCs, regardless the serum calcitonin levels and preoperative examinations of regional LNs, has led many surgeons to do prophylactic lateral neck dissections (LND). The aim of this study was to analyze usefulness of sentinel lymph node biopsy (SLNB) of jugulo-carotid regions, after methylene blue dye (MBD) mapping and frozen section analysis, for selecting true positive patients in clinically N0 (cN0) group of micro-MTCs for one-time LND.
Methods
In a 10-year period, 17 cN0 patients were operated by our surgical team due to micro-MTCs ($\leq$10 mm), with serum calcitonin <1000 pg/ml. In all patients, sentinel-LN mapping was performed by injecting 1%-MBD subcapsullary in both lobes. As a standard surgical treatment, along with total thyroidectomy and prophylactic central neck dissection, all patients had SLNB of jugulo-carotid regions (*Dzodic's original method for LN staging in thyroid carcinomas*, published in *World J Surg, 2006*), since blue-stained LNs in central compartment are routinely dissected. After exploration of levels II-III bilaterally, sentinel-LNs were extirpated and examined by frozen section. If sentinel-LNs were benign, additional surrounding non-sentinel-LNs were extirpated and sent to standard pathohistology (sPH), with no further LND. If sentinel-LNs were malignant, one-time LND was performed.
Results
One patient with calcitonin level of 221 pg/ml had hereditary, bilateral micro-MTC, positive central-LNs and sentinel-LNs on both sides, so bilateral LNDs were performed. Metastases were found in non-sentinel-LNs, as well, thus sentinel-LNs were predictive for non-sentinel-LNs status. Remaining 16 patients had sporadic, unilateral micro-MTCs, without metastases in central-LNs, sentinel-LNs or additional LNs from levels II-III on both sides. None of the patients had allergic reactions to MBD. Frozen section and sPH were 100% match. Accuracy of *Dzodic's method for LN staging* was 100%.
Conclusions
This study is the first reported experience with SLNB of jugulo-carotid regions in MTCs using MBD, focusing on the subgroup of microcarcinomas. The *Dzodic's method for LN staging* in thyroid carcinomas can be precisely used for intraoperative assessment of lateral-LNs and optimizing initial surgery of micro-MTCs. cN0 patients with proven sentinel-LN metastases in lateral regions on frozen section can receive one-time LND, while those without LN-metastases benefit from less extensive surgery. All patients can benefit from lower complication rate, since MBD injection facilitates central neck dissection and diminishes the possibility of accidental removal of parathyroid glands (that remain non-colored), even in less experienced surgeons' hands.

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Poster Presentations: Calcium and Bone

Bone & Osteoporosis

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Influence of the levels of vitamin D on T-score in HIP measured by DXA of colombian postmenopausal women

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Introduction
The 25hydroxyvitamin(OH)D deficiency has been linked to the risk of postmenopausal fractures and osteoporosis. In Colombia, the prevalence of 25(OH)vitaminD deficiency is high, reaching more than 53% of the total population. It can be stated that hip fracture is one of its most feared complications, with a high risk of mortality and morbidity, which can affect even osteopenic patients. The objective of this study is to assess modifications in hip T-score (using dual-energyX-ray absorptiometry(DXA)), that are related and influenced by changes in 25(OH)vitaminD levels in Colombian postmenopausal women.
Methodology
This study is a cross-sectional analysis that uses linear regression to determine the changes of hipT-score value (standard deviation(SD)) according to vitaminD levels, it is adjusted to serum calcium, phosphorus, paratohormone levels and age. To establish the validity of the model: the homocedasticity and normality of the residues were exhibited; Cook's distance <2 and colinearity was ruled out (VIF $<$ 10). VitaminD deficiency was defined as a value of 25(OH)vitaminD below 20 ng/ml (50 nmol/l), and vitaminD insufficiency as a value between 21 and 29 ng/ml(3).
Results
124 Postmenopausal women were included at mean age of 66.07 ± 11.28 years; with average levels of serum calcium:9.53 ± 0.60 mg/dl; mean of paratohormone:57.06 ± 27.14 pg/ml; mean vitamin25(OH)D:25.69 ± 9.22 ng/ml; mean serum phosphorus: 3.62 ± 0.61 mg/dl; mean hip T-score: $-1{,}92 \pm 1{,}18$; mean hip Z-score:$0{,}058 \pm 0{,}80$; hip bone mineral density:$0{,}833 \pm 0{,}095$;g/cm^2; 22.08% of patients had a deficiency of 25(OH)vitaminD and 53.25% had insufficiency of 25(OH)vitaminD; 31% of patients had osteoporosis and 53% osteopenia. The linear regression model found that a 25 (OH) vitamin D change of 0.042 ± 0.20 ng/ml (95% CI 0.012–0.083, $P=0.04$) produces a change of 1 (one) standard deviation in hip T-score; adjusting to levels of paratohormone, serum calcium, serum phosphorus and age; constant value -6.34.The linear regression equation would be:HipT-score $= 6.34 + 0.042$(25(OH)vitaminD). The model explains 22% of the changes in the T-score, the residuals were homocedastic and normal ($P=0.70$); there was no collinearity (average VIF $= 1.11$) and distance of cook $=$ 0.064.
Conclusion
This study tries to demonstrate how very small variations in the levels of 25(OH) VitaminD, can significantly influence changes of up to 1(one)SD in hip T-Score of postmenopausal women.

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Potential extension of frax algoritm and probability of bonefracture

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Osteoporosis is a pandemic chronic non communicable disease, with worldwide expansion. This condition and the resulting bone fracture are a maor cause of disability and mortality for millions of people worlwide. Frax is an algoritm that relies on a questionnaire for the prediction of bonefracture. This algoritm it is called Frax and it's estimates the probability in % to have a fracture in the following 10 years. The aim of the study was to evaluate whether patients lifestyle and dietary habits may be considered as additional risk factors for new bone fracrtures and evaluate how its correlates to the degree of osteoporosis, Furthermore we analysed if obesity can be associated with reduced levels of bone mineral density (BMD). IN tha last year we have enrolled 1132 patients at the Unit of Endocrinologia, Diabetes and Metabolic Diseases at the University Hospital of TOr Vergata, Rome, Italy. All subjects underwent to evaluation of anthropotric data (weight, BMI, height), bone densitometry with DEXA Hologic QDR 4500 Delphi series, Food frequency questionnaire to access dietary habits during a week and Frax questionnaire. From 1132 subjects, the media of the age was 63.3 (± 9.5 s.d.); from wich 1086 were women (63.3 years ± 9.4 s.d.) and 45 men (63.8 years ± 11.6 s.d.). The food questionnaire data when divided considering the T-score in three groups, 210 subjects normal (-0.29 s.d. $\pm$ 0.636/0.818 g/cm^2/± 0.07), 712 with osteopenia (-1.74 ± 0.42/0.649 g/cm^2 $\pm$ 0.05) and 210 with osteoporosis (-2.86 ± 0.38/0.515 g/cm^2 ± 0.04), confirming that patients with osteoporosis, consume less foods that contains calcium and vitamin D (p value 0.01). Patients were also divided according the body mass index (BMI). From 1132 people the 0.79% were underweight (9 subjects), 34.8% (395 subjects) have normal weight, 36.7% (416 subjects), overweight (27.2 ± 1.4) and 27.5% (312 subjects) were obese (33.7 ± 3.7). It is important to consider that the prevalence of oveweight and obesity in our population was 64.2%. if then we analyze the patients that were overweight and obese, the majority of the sample (80%) presents osteopenia of osteoporosis; this result is controversy from the supposed protective role of adipose issue on bone mineral density.

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A case report: FGF23-related tumor-induced osteomalacia in a patient with pulmonary adenocarcinoma

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Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome caused by the abnormal production of fibroblast growth factor 23 (FGF23) in the tumor. Here we report a case of TIO with pulmonary adenocarcinoma. A 61-year old woman was referred to our hospital. She was suffering from severe polyarthralgia and bilateral limb weakness. Her blood chemistry revealed high alkaline phosphatase, low phosphate, low calcium, and low 1,25-$(OH)_2D_3$. Bone-scintigraphy revealed multiple accumulations in femoral neck, sacrum, 1st rib, sacroiliac joints and many other joints, suggesting small fractures and systemic arthritis. Endocrinological analyses exhibited elevated iPTH and markedly high FGF23 level of 3900 pg/ml (reference: 14.7–40.5 pg/ml). These findings suggest that the FGF23-producing tumor of uncertain location induced osteomalacia in this patient. DOTATOC-PET/CT showed a major uptake in a nodular lesion of the left lung and several minor uptakes in the supraclavicular, hilar and mediastinal lymph nodes. An ultrasound-guided fine needle aspiration biopsy of the left supraclavicular lymph node was performed and the histological diagnosis was metastatic adenocarcinoma. PNA-LNA PCR clamp analysis of the biopsy specimen detected a mutation in Exon19 of the EGFR gene. She was diagnosed as stage IVA (cT1cN3M1b) pulmonary adenocarcinoma, and the chemotherapy with afatinib maleate (EGFR tyrosine kinase blocker) was started. At the same time, alfacalcidol was prescribed for osteomalacia. After 5 months, the primary tumor and metastatic lesions are gradually shrinking. The bone metabolism is almost normalized, and FGF23 level is markedly decreased (42 pg/ml). At present, the arthralgia is ameliorated and controlled with minimal dose of analgesics. This is a rare case of TIO associated with pulmonary adenocarcinoma. The DOTATOC-PET/CT was an effective modality for diagnosis.

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Abstract withdrawn.

P168

Features of distal forearm fracture in persons 50 years old and older

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Objective
To identify the prevalent fracture risk factors in the group of persons 50 years and older. Assess their impact on BMD in patients with a distal forearm fracture (DFF-fracture of the radius) over 50 years at low injury.
Materials and methods
A comparative study among patients with DFF in the age group 50 years and older. Study based on medical records of city hospital traum depatment. Analised period 2009–2012. All patients underwent R-densitometry on the unit DTX-200, provided by Nicomed Takeda in the framework of the program 'Russian Osteoscreening'.
Results
Hospital records of patients 50 years and older who suffered from low-energy fracture of the distal forearm were analyzed retrospectively for the period of 2009–2012. 791 patients were interviewed using standardized questionnaires 'Osteoscreening Russia'. According to the survey the metabolic syndrome (MS) diagnosed in 70.8% (560 persons). It included type 2 diabetes mellitus (T2DM) −14.8% (117 persons), prediabetes −22.9% (181 people) – (Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)), obesity (33.1%) – an isolated cohort of patients with overweight and obesity without disrupting glycemic indices. All patients had DFF that occurred at a low injury. Among the investigated cohort of patients with highnormal bone mineral density (BMD above −1.0 standard deviation (S.D.))we revealed 66.0% of patients with MS; 64.1% – with obesity; 65.4% – with the presence of pre-diabetes; 65.3% – with a history of type 2 diabetes. BMD−1.0–2.5 S.D.: 20.6% with MS; obesity, 20.2%; prediabetes, 19.7%; type 2 diabetes −19.5% BMD below 2.5 standard deviations (S.D.): MS at 13.5%; obesity, 15.7%; prediabetes, 14.7%; Type 2 DM −15.3%. Patients with low-energy DFF with a history of metabolic syndrome differed from the group of patients without this disease by its high and highnormal % normal BMD. Almost 2/3 (70.8%) of patients with metabolic syndrome have normal BMD.
Conclusion
The prevalence of low BMD in patients of investigated groups has not been established. Proposed mechanism of fracture is focused not on the performance of T-score (BMD) but the bone quality due to changes caused by abnormality of bone metabolism. Suppression of medullary osteoblastogenesis by adipocytes of bone marrow and stimulation of proinflammatory cytokines synthesis leads to increased bone fragility without decreasing BMD.

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Effect of surgery vs observation: 6-Year skeletal outcomes in primary hyperparathyroidism

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Background and aims
Primary hyperparathyroidism (PHPT) often presents without classical symptoms such as overt skeletal disease or nephrolithiasis. Treatment strategies have been widely discussed. The objective of our research was to study the effect of parathyroidectomy (PTX) compared to observation (OBS) on skeletal outcomes such as bone mineral density (BMD).
Subjects and methods
A retrospective observational study was conducted between 1991 and 2014. 170 patients with PHPT who had baseline dual energy x-ray absorptiometry (DXA) and at least another one after 2 years of follow-up were included. Mean follow-up time was 6 years. PHPT was diagnosed when persistent hypercalcemia occurred with the presence of elevated or inappropriately normal parathyroid hormone levels. Clinical features were registered. Area based BMD was measured by at the lumbar (L2–L4) spine (LS), femoral neck (FN), total hip, and forearm at the radius 33% (Rad33).
Results
112 patients were treated with PTX and 58 patients were under OBS. Patients under OBS were older than PTX group, mean age 68.8±12.1 years and 62.5±11.3 years respectively ($P<0.005$). More than 85% of patients in both groups were women. DXA after two years of surgical intervention showed a mean BMD change of 4.37% in LS, 3.9% in FN, and 2.72% in the total hip. Significantly higher than those presented at 2 years in the observation group (1.59% in LS, −0.19% FN, 0.14% CT) ($P<0.005$). In Rad33, BMD remained stable in the PTX group and decreased in OBS group ($P=0.583$). At 4 and 6 years, a positive effect of PTX was still observed with statistically significant improvements in the LS and FN ($P<0.05$). In total hip and Rad33, improvement was observed with PTX and worsening in the OBS group, but these differences were not statistically significant. It is important to note that 58% of patients in PTX group and 63.8% of patients in OBS group received treatment with drugs with bone activity, mainly bisphosphonates according to the criteria of their physician. Anyway it may have reduced, but not increased, the difference between groups.
Conclusions
In conclusion, PTX improves BMD and OBS leads to a small, but statistically significant decrease in BMD in FN. The surgical intervention does not involve significant changes in Rad33 BMD. Thus, bone health appears to be a clinical concern with long-term observation in patients with mild PHPT.

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Association between Serum FGF21 levels and bone mineral density in healthy postmenopausal Korean women

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Objective
Despite beneficial effect of FGF-21 on metabolic disease, there were concerns about adverse effect on bone metabolism, supported by animal studies. However, a recent human study showed the positive association between FGF-21 and bone mineral density (BMD) in health premenopausal women. This study was undertaken to examine the association between FGF-21 and BMD in healthy postmenopausal Korean women who are susceptible to osteoporosis.
Methods
We used data of 115 participants from healthy postmenopausal women cohort (>50 years old) to examine the correlations between FGF-21 levels and BMD. Participants had provided information regarding their clinical characteristics, and underwent blood testing and serum FGF-21 testing. BMD and T scores of lumbar spine, femur neck and total hip area were used in analyses.
Results
The subjects' mean age was 60.2±7.2 years old and mean BMI was 24.4±3.5 kg/m^2. The prevalences of osteoporosis were 19.6%. There were two patients with a history of lumbar fractures and none had a history of hip fractures. Serum FGF-21 level showed inverted correlation with BMD and T scores at all three areas; however, there were no statistical significances. Multivariate analyses with adjustment for age and BMI also did not show significant associations of FGF-21 level and BMD and T scores. Additionally, FGF-21 level also showed no correlation with CTX and osteocalcin.
Conclusions
In our study, serum FGF-21 level showed no significant correlation with BMD and T scores.

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Bone geometry is correlated with arterial stiffness in overweight older adults with vitamin D insufficiency

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Background
Vitamin D deficiency/insufficiency and adiposity have deleterious effects on skeletal health and can increase arterial stiffness. Additionally, low bone mass is associated with increased arterial disease, but little is known about the association of bone geometry with arterial disease.
Objective
To determine the association between bone geometry and arterial stiffness in overweight (body mass index >25 kg/m^2], older adults [50–80 years] with vitamin D insufficiency [<50 nmol/l].
Methods
Cross-sectional analysis. Demographics and clinical history were obtained via questionnaires and anthropometric data were obtained using standard protocols. Tibial bone geometry in the tibia at the 4% and 66% sites was assessed via peripheral quantitative computed tomography [XCT3000, Stratec, Germany]. Blood pressure and measures of arterial stiffness were determined by an oscillometric device [Mobil-o-Graph, IEM, Germany]. These measures included pulse wave velocity [velocity at which arterial pulse propagates throughout the vasculature], augmentation index [proportion of blood pressure waveform attributable to the reflection wave] and pulse pressure [difference between systolic and diastolic blood pressure]
Results
Thirty individuals were recruited [mean age: 57.7 ± 6.3; women: $n=15(50\%)$]. Mean systolic blood pressure was high-normal [128.6 ± 13.5 mmHg]. In age and BMI adjusted models, there was an inverse correlation between trabecular area at 4% site [$r=-0.80$; $P<0.001$]; trabecular volumetric bone mineral density [$r=-0.58$; $P=0.003$]; cortical area at 66% site [$r=-0.55$; $P=0.008$]; fracture load(x) [$r=-0.47$; $P=0.028$]; fracture load(y) [$r=-0.69$; $P<0.001$] with augmentation index. Additionally, there was an inverse correlation between trabecular area at 4% site [$r=-0.42$; $P=0.027$] and cortical area at 66% site [$r=-0.449$; $P=0.018$] with pulse pressure. Bone marrow density correlated positively with pulse pressure [$r=0.448$; $P=0.021$]. In multivariate regression analyses adjusting for age, BMI and sex, trabecular area was inversely associated with augmentation index [$\beta=-5.67$; 95% confidence interval: -8.81, -2.43].
Conclusion
Poorer bone geometry was strongly negatively related with augmentation index, a measure of systemic arterial stiffness. This provides further evidence for an association between bone loss and changes in arterial stiffness that act to increase vascular risk. A randomised trial is now required to determine if an intervention to reduce underlying adiposity and correct vitamin D deficiency will improve these outcomes.

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Effects of acromegaly on plasma microRNA levels relevant to bone metabolism.

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Molecular basis of the bone disorders in patients with acromegaly are largely unknown.
Objective
To investigate microRNAs (miRNA) expression profiles that regulate bone metabolism in plasma samples from patients with acromegaly.
Materials and methods
Fasting plasma samples were taken from consecutive subjects with biochemically confirmed active acromegaly and healthy volunteers matched by age, sex and BMI. IGF1 was measured by an electrochemiluminescence assay on a Liaison. Total RNA isolation from plasma samples with on-column digestion of the genomic DNA was carried out with miRNeasy Mini Kit on the automatic station 'QIAcube'. Reverse transcription was carried out using a TaqMan Advanced miRNA cDNA Synthesis Kit. MicroRNA expression analysis was performed by Real-Time PCR on StepOnePlus instrument with TaqMan Advanced miRNA Assay.
Results
22 subjects with acromegaly mean age 40 (CI 95% 36–44) years old, 17 females and 5 males, BMI – 28 (CI 95% 25–31) kg/m^2 were enrolled along with 18 healthy control subjects (17 females, 1 male) matched by age $P=0.205$ and BMI $P=0.253$. Mean IGF-1 in subjects with acromegaly – 752 (CI 95% 577–926) ng/ml was higher as compared to healthy control – 195 (CI 95% 139-251) ng/ml ($P<0.001$). Among the 28 miRNAs studied, expression of miRNA-320a 12.2 (CI 95% 4.3 – 20.2, $P=0.056$) was increased in patients with acromegaly as compared to healthy volunteers. The revealed change negatively affects the level of β-catenin and Runt-related transcription factor 2 (RUNX2) and promotes suppression of chondrogenesis. However, after applying the correction of multiple comparisons, the change in the level of miRNA-320a was statistically insignificant ($q=0.605$), which is most likely due to the insufficient sample size.
Conclusion
Plasma miRNA-320a can be considered as a potential diagnostic marker of osteoporosis.

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Is FGF23 a key factor in primary hyperparathyroidism?

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Published data regarding the role of FGF23 in primary hyperparathyroidism and its prognostic applicability are scarce and discordant.
Aims
To assess FGF23 profile in patients with primary hyperparathyroidism undergoing surgery.
Matherials and methods
Longitudinal study involving 48 patients aged 30–80 years with primary hyperparathyroidism caused by solitary parathyroid adenoma, submitted to parathyroidectomy. We evaluated FGF23, PTH, 25(OH)D3, calcium and phosphorus at admission, immediately after parathyroid adenoma excision in all patients, and at 3, 6 months and one year after surgery in 13 patients. Differences were considered significant for $P<0.05$.
Results
FGF23 was within the reference ranges (120 ± 80 pg/ml, normal values specific for carboxyterminal FGF23, dosed in this study), with initial mean values of 75.55 ± 22.74 pg/ml. Preoperative FGF23 was negatively correlated with PTH ($r=-0.397$; $P=0.015$) and calcium ($P=0.04$). We observed no change in postoperative FGF23 or at distance from cure (80.57 ± 27.07 pg/ml 1 year postoperative, NS). Mean FGF23 did not show significant differences in patients with osteoporosis, renal lithiasis or fractures, neither preoperatively, nor 1 year after surgery.
Conclusions
FGF23 levels of patients with primary hyperparathyroidism are in the normal range and do not change significantly after surgery seeming therefore to have no practical prognosis application. The negative correlation of FGF23 with preoperative PTH seems to be an epiphenomenon and suggests that FGF23 regulating role may be largely replaced by PTH in primary hyperparathyroidism.

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Long-term monitoring of echinococcal cyst as a cause of increased lumbar bone mineral density

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An 82-year old female with known osteoporosis was reassessed for bone mineral density (BMD) measurement. Her baseline BMD and lumbar spine T-score (L1-L4) measured in 2004 was 0.699 g/cm^2, –3.5 SD, total left hip T-score was 0.618 g/cm^2, –2.7 SD. She was treated with alendronate 70 mg, cholecalciferol 7000 IE per week and calcium supplements for some years. On follow-up in 2013

DXA of lumbar spine and hip, BMD of lumbar spine L1-L4 was 0.910 g/cm^2, T-score was –1.2 SD. BMD and lumbar vertebrae T-scores for a single lumbar vertebra were: L1 1.384 g/cm^2, +4.2 SD; L2 0.667 g/cm^2, –3.3 S.D.; L3 0.654 g/cm^2, –3.9 S.D.; L4 0.785 g/cm^2, –3.0 S.D. The BMD and T-score of the neck were 0.463 g/cm^2, –3.5 S.D. and of the total hip 0.590 g/cm^2, –2.9 S.D. The images revealed a calcified mass in the L1 vertebral projection. The DXA scan analysis was repeated and the calcified formation in the L1 vertebra was excluded. BMD of analyzed lumbar spine (L2–L4) was 0.701 g/cm^2, T-score was –3.4 S.D. BMD and T-scores were: L2 0.614 g/cm^2, –3.8 S.D.; L3 0.642 g/cm^2, –4.0 S.D.; L4 0.785 g/cm^2, –3.0 S.D. In 2018, BMD of analyzed lumbar spine (L3–L4) was 0.911 g/cm^2, T-score was –1.7 S.D. BMD and T-scores were: L3 0.976 g/cm^2, –1.0 S.D.; L4 0.845 g/cm^2, –2.5 S.D., superposition of calcified formation was on L1 + L2. Abdominal CT scans revealed a 3 cm large calcified Echinococcal cyst (EC) that was unnoticed in 2004. 2013 DXA scans show the EC projected to the L1 and those made in 2018 EC is seen on L1 + L2 + L3 because of the development of kyphosis, and consequently due to height reduction of 9 cm over the period of 14 years. Hip BMD was stable; the 10-year fracture risk for major osteoporosis fracture was 16% and 7.5% for hip fracture. Discussion. The study showed that calcium carbonate pills and bra wires positioned lateral to the spine can change BMD. Several medical conditions, such as osteoarthritis, ankylosing spondylitis, vertebral fractions, osteophyte formation, and aortic calcifications can also increase BMD. In our case, the patient's hip BMD decreased by –1.8% and increased by 51.3% in L1-L4 without corrections on account of EC in the period of 14 years.

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Acromegaly patients with vertebral fractures, have lower trabecular bone score despite no difference in bone mineral density, than non-fractured patients and healthy controls

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Introduction
Patients with acromegaly, despite normal or even high bone mineral density (BMD), have prevalent vertebral fractures (VFs). HR-pQCT studies in acromegaly have proposed that impaired trabecular bone microarchitecture possibly plays a role in fragility fracture development. As such, we hypothesized that trabecular bone score (TBS) would be low in patients with acromegaly.
Aim of the study
To compare BMD and TBS in acromegaly patients with and without VFs and healthy controls.
Methods
This cross-sectional study compared patients with acromegaly to age- and BMI-matched healthy controls. Study group was recruited from all acromegaly patients who came to a University Endocrinology clinic for follow-up from 6/2016 – 8/2017 and controls consisting of healthy subjects. In all subjects a single measurement of pituitary axis hormone levels, P1NP,CTx, BMD, (total hip [TH] and lumbar spine [LS]) and trabecular bone score (TBS) was performed. Vertebral fractures were identified by DXA VFA. These images were interpreted by an expert musculoskeletal radiologist (H. Genant) using a semi-quantitative approach.
Results
One-hundred six patients with acromegaly (mean age 56.6 years, mean BMI 30.2 kg/m^2) and 104 control subjects (mean age 54.06 years, mean 28.4 BMI kg/m^2) were included. There was no difference in TH BMD, CTx and plasma cortisol between study groups. Patients with acromegaly had lower LS BMD (1.002 ± 0.16 vs 1.049 ± 0.15; $P < 0.05$) and TBS (1.19 ± 0.13 vs 1.33 ± 0.14; $P < 0.0001$). higher levels of IGF-1 (244.5 ± 189.2 vs 115.2 ± 37.7 ng/ml; $P < 0.0001$) and P1NP (55.69 ± 34.3 vs 45.47 ± 18.6 ng/l; $P < 0.05$). In total, 13 patients and 4 control subjects had VFs identified using IVA. Among acromegaly patients those with VFs had lower TBS (1.11 ± 0.12 vs 1.20 ± 0.13; $P < 0.05$) and P1NP (32.06 ± 16.9 vs 58.5 ± 34.9 ng/l; $P < 0.05$) levels than non-fractured. No difference in BMD (both measured sites), CTx or IGF-1 was observed.
Conclusions
In this study, acromegaly patients had lower TBS and LS BMD than healthy controls. Additionly, those with VFs had lower TBS, and P1NP, but not BMD (both measured sites) than non-fractured acromegaly subjects. Thus, it could be suggested that VFs in acromegaly subjects are associated with impaired trabecular microarchitecture. We suggest using TBS, rather than BMD, to identify acromegaly patients at high VF risk.

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Atypical femoral fracture-a possible complication in long term use of bisphosphonates (case report)

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One of the clinical complications associated with the long term use of bisphosphonates treatment in osteoporosis is the atypical femoral fracture (AFF).Even the absolute risk is low and acceptable compared with the number of fractures prevented, there are still reasonable concerns due to the wide prescription of bisphosphonates and the existence of several case series proving that bisphosphonates have a strong association with this unique fracture type. We present a case of a 81 year old woman who was admitted in our clinic two and a half years ago right after she was treated for left femoral fracture in the orthopedic department.She had no history of recent trauma or low energy trauma,no corticotherapy, smoking or alcohol intake,no previous fractures.For the past 13 years she was continously treated with various type of bisphosphonates without any therapeutical pause or medical control.At that moment an association between bisphosphonates long term use and the occurence of atypical femoral fracture has been suggested.This diagnostic has also been supported by the X-ray with all the major features of AFF.Therapy with strontium ranelate and vitamin D supplements was initiated right after surgery with fully recover of the mobility and an increase in the quality of life. While concrete evidence based recommandations canot be provided, strict surveillance,overall awareness of prodromal thigh pain,radiological findings and bisphosphonates usage records are recomanded for prevention.For most people with osteoporosis the proven fragility-fracture risk-reduction benefits of bisphosphonates outweigh the risks of AFF.

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Malignant hypercalcemia induced by denosumab discontinuation in a patient with primary hyperparathyroidism

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Context
Denosumab, a fully human monoclonal antibody that inactivates receptor activator of nuclear factor k-B ligand (RANKL), is used for osteoporosis treatment because of its potent anti-resorptive properties. Due to its reversible mode of action, bone resorption increases rapidly after its discontinuation and is accompanied by a quick loss of bone mineral density. Spontaneous vertebral fractures at this period have been recognized as secondary to the rebound of bone resorption. Three cases of rebound-linked hypercalcemia have also been

described, one of moderate hypercalcemia following denosumab discontinuation given for osteoporosis, and 2 cases of malignant hypercalcemia in children receiving oncologic doses of denosumab.
Case report
We report the case of an osteoporotic 86-year-old woman treated with denosumab 60 mg subcutaneously every 6 months from 2013 to October 2016 (last injection). She is also known for a primary hyperparathyroidism (PTH 24.2 pmol/l, NV 1.3-9.3), with serum corrected calcium (CCa) at 2.82 mmol/l (NV 2.15-2.5) in April 2017, at the end of denosumab efficacy. Treatment by 30 mg/day cinacalcet lowers CCa to 2.51 mmol/l one month after. In July 2017, she is hospitalized due to weight loss (5 kg,15% body weight), malnutrition and bad health status. Clinical evaluation concludes to malignant hypercalcemia (CaC 3.53 mmol/l) despite lower PTH (10 pmol/l). Initial treatment by hydration and intranasal calcitonin only partially corrects CCa to 2.95 mmol/l. Very high values of bone resorption markers (B-crosslaps 1777 ng/l, NV $<$573; creatinine 97 umol/l) suggest a rebound effect due to denosumab discontinuation. An X-ray shows new multiple vertebral fractures. After injection of 60 mg denosumab, CCa rapidly lowers to 2.63 mmol/l, and bone resorption markers dramatically decrease (122 ng/l B-crosslaps).
Conclusion
This critical case suggests that hypercalcemia is an underappreciated side effect of denosumab discontinuation, which can become a severe complication when other causes of hypercalcemia, like primary hyperparathyroidism, are present.
Keywords: Bone turnover markers. Denosumab discontinuation. Hypercalcemia. Osteoporosis.
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An extremely high risk of recurrent fractures in an elderly patient, identified with the implementation of Fracture Liaison Service (FLS) in a trauma hospital.

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Introduction
Osteoporosis is a serious problem all over the world. The presence of low-energy fractures increases the risk of repeated fractures twice. Each new fracture increases the risk of a fatal outcome in the future. Globally, the most effective model of re-fractures preventing in patients with osteoporosis is a Fracture Liaison Service (FLS). FLS main objectives are identification of patients, assessment of re-fractures risks, diagnosis and initiation of osteoporosis therapy. In our hospital, this service has been operational since 2017.
Clinical case
Woman, 72 years old, with a fall from the height growth, suffered a fracture of the left proximal shoulder. She was hospitalized in the trauma department of the City Clinical Hospital No. 13. This fracture in the patient is not the first. In 2015, she underwent several compressive vertebral fractures. Currently, anti-osteoporotic drugs do not take. Also, suffers from rheumatoid arthritis. The onset of menopause in 50 age. When examining: there is curvature of the spine by type 'widow's hump'. Growth of 146 cm (decreased by 10 cm in height), 46 kg of BMI 21.6 kg/m^2. According to laboratory tests: vitamin D deficiency was found to be 8.4 ng/ml ($<$20-deficiency), an increase in the level of alkaline phosphatase 179 (0–120) U/l. The rest of the laboratory parameters were within norms: calcium 2.26 (2.15–2.55) mmol/l, phosphorus 1.38 (0.81–1.45) mmol/l, parathyroid hormone 82.4 (12.0–88.0) pg/ml, creatinine 46 (44–80) umol/l. The result of densitometry (DEXA): severe systemic osteoporosis with a very significant loss of bone mineral density. (T-score L1-L4 -4.5, neck of the left hip -4.4). But the worst result was in calculating the risk of repeated fractures with the FRAX® Calculation Tool, which showed a more than 50% chance of recurrent fractures and a 32% chance of a hip fracture (this is an extremely high risk). In connection with this, the patient began to take the prescribed pathogenetic anti-osteoporotic therapy and supplements of calcium and vitamin D immediately, in the hospital. We hope that the treatment started will reduce such high risks and protect against the most dangerous fracture of the hip.
Discussion
The introduction of the FLS into the practice of the City Hospital in Moscow is real and justified. This will help identify patients with the highest risks and will allow timely initiation of anti-osteoporotic therapy, thereby reducing the risks of fractures in the future.
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The comparison of parathyroid neoplasms mappings evaluated by using gray scale ultrasound images and histopathological whole slide images

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Aim
The aim of this study is to correlate the histopathological cell types and morphologic features of parathyroid neoplasms with ultrasound(US) images and laboratory findings, and also gain more information about the clinical importance of these results.
Materials and methods
The parathyroid lesions of 57 patients who were operated for hyperparathyroidism were sampled on saggital plane. The slides were scanned on high resolution and digital whole slide images were formed. The system was consisted of motorized microscope, motorized table, robotic slide loader, and a high resolution camera. The slide on the motorized table was automatically scanned with the chosen objective and a high resolution image was formed. This image was opened with the help of an interface and then examined. These images can be archived. The US and the slide images were matched by the manufacturer software program.
Results
Forty three patients were female (73.7%). The ages of the patients were between 21–48 years and the median was 53. The study population had 47 adenomas, 7 atypical adenomas, 2 carcinomas. The median of parathormone (PTH) was 194 pg/ml (min–max: 53–2800), median of the tissue area was 96.29 (min–max: 16.01–576.05). Hypoechogenic areas on ultrasound(US) were matched with chief cells in 21 (55.3%), oncocytic cells in 2(5.0%), cyctic morphology in 8(20.0%) cases. There were less chief cells and more connective tissue in hyperechogenic areas ($P<0.05$). Hyperechogenic areas had less clear cells than isoechoic areas ($P<0.05$). Lipoic tissue ratio was significantly less in hypoechoic areas than hyperechoic areas ($P<0.05$). There was no significant difference between echogenicity, oncocytic cells, and haemorrhagia. There was a significant positive correlation between PTH and total neoplasm area ($r=0.377$, $P=0.004$). There was no significant difference between cyctic area ratio and chief cell amount in atypical and other cases($P>0.05$). A moderate positive lineer relationship was found between serum calcium levels and cyctic area ratio and percentage ($r=0.416$, $P=0.048$).
Conclusion
The morphologies of parathyroid neoplasms taken from the digital whole slide images were compared to US projections in the study. However, hypoechogenic areas of US images were matched with chief cells, hyperechogenic areas were compatible with connective and adipose tissues in histopathology. The positive lineer relationship between serum calcium levels and cyctic areas was open to new researches. Results of this study may guide the evaluation of the clinic outcomes of detailed morphometric studies with digital whole slide method.
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P180

Evaluation of bone mineral density and vertebral fracture incidence in a group of kidney transplant recipients

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Kidney transplant patients are prone to metabolic bone diseases. In this descriptive clinical study we aimed to evaluate the incidence of osteopenia osteoporosis, vertebral fractures in our group of renal transplant patients.
Methods
Eighty seven patients (25 males and 62 females) aged from 20 to 67 years, who had undergone kidney transplantation 1 to 20 yrs. previously included in the study. Bone mineral densitometry was performed using dual-energy X-ray absorptiometry, Thoracolumbar lateral vertebral X-ray evaluated for fracture according to Genant classification. Serum parathormone (PTH), 25OH vitamin D, calcium, phosphate, Luteinizing hormone (LH) and Follicular stimulating hormone (FSH) levels were measured.
Results
The incidence of osteoporosis was 26% (23 of 87 patients).and osteopenia was 52.8% (46 of 87 patients). Vertebral fracture was observed in 28.8% of the patients in thoracolumbar lateral vertebral X-ray evaluation. Serum Ca and P levels were in normal range while PTH levels were elevated and 25OH vitamin D levels were in deficient range. Vertebral fractures mostly observed in patients with osteopenia (17.2%). A negative correlation with post-transplantation duration with serum PTH levels (r: -0.16 $P<0.05$) and femur neck BMD (r:-0.24, $P<0.03$) was observed. Femur and lumbar 1-4 BMD levels were negatively correlated with serum LH and FSH levels ($P<0.001$).
Conclusion
Vertebral fractures observed more frequently in osteopenic group of renal transplant patients. Besides the BMD evaluation, vertebral fracture evaluation may help to make a proper therapy decision for metabolic bone disease in kidney transplant receipents

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P181

PTH correlates with bone turnover serum markers in patients with end stage renal disease

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Background
End stage renal disease is usually associated with high serum parathyroid hormone (PTH) and increased bone turnover. The aim of our study was to correlate serum PTH with serum markers of bone turnover in patients with end stage renal disease (ESRD).
Methods
We measured serum PTH, osteocalcin, procollagen type 1 n-terminal propeptide (P1NP) and beta-crosslaps in 64 (32 men) consecutive pacients, median (25, 75 percentile) age 61 (49.5, 65.5) years, on permanent hemodialysis.
Results
Median (25, 75 percentile) PTH, osteocalcin, P1NP and beta-crosslaps were 246.1 (128, 487.9) pg/mL, 233.9 (96.7, 300) ng/mL, 287.1 (169.9, 810.7) ng/mL and 2.25 (1.63, 3.25) ng/mL, respectively. 90.6%, 96.8% and 93.7% of osteocalcin, P1NP and beta-crosslaps results respectively were higer than the upper limit of normal. We found a positive correlation between serum PTH and bone formation markers osteocalcin ($r=0.6136$, $P<0.001$) and P1NP ($r=0.6898$, $P<0.001$). There was no correlation between PTH and bone resorbtion marker beta-crosslaps ($r=-0.1520$, $P=0.23$).
Conclusion
Bone turnover is increased in end stage renal disease. Beside PTH, osteocalcine and P1NP could also be associated with osteitis fibrosa of ESRD.

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P182

Rapid washout in primary, secondary, and tertiary hyperparathyroidism and utility of dual radiopharmaceutical acquisition with ^{99}Tc-sestamibi-^{123}I for localization of parathyroid adenomas

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^{99m}Tc-Sestamibi (SeS) is a standard tool for localization of adenomas/hyperplasia (PA) in hyperparathyroidism (HPTH), designed on the difference between thyroid and parathyroid tissue radiotracer washout on early and late scintigraphy phases. However, PA have been reported to washout as fast as normal thyroid tissue ('rapid washout', RW), which may lead to diagnostic failure. The aim of the study was to determine a correlation of RW of SeS from parathyroid glands and types of hyperparathyroidism (HPTH). The utility of dual isotope radiopharmaceutical acquisition with ^{123}I/SeS subtraction imaging (SS) for detection of PA with RW was also investigated.
Methods
An IRB approved retrospective review of cases with HPTH referred to nuclear medicine and had subsequent parathyroid surgery was performed. Pre-, post-surgical and biochemical workup of HPTH, surgical pathology reports were analyzed. Correlative imaging with ^{123}I/SeS subtraction imaging was performed on selective patients. Group comparison was performed using paired t-test, ANOVA, and Brown–Forsythe tests.
Results
135 HPTH patients after parathyroidectomy with available dual phase SeS, pathology report, pre- and post-surgical biochemical HPTH workup were analyzed. Ninety-six (71%) patients had primary (p-HPTH), 29 (21%) had secondary (s-HPTH) and 10 (7%) had tertiary (t-HPTH) HPTH. 87/103 (84%) in p-HPTH, 53/94 (56%) in s-HPTH, and 16/23 (69%) in t-HPTH glands were positive on late SeS. RW was identified in 27% (28/103) p-HPTH, 15% (14/94) s-HPTH, 4% (1/23) t-HPTH ($P<0.0001$). Glands that were positive on late SeS phase were large being 1.7 (IQR: 1.4–2.3) vs 1.45 (IQR: 1–2) cm ($P=0.0036$). Median PTH levels for p-HPTH, s-HPTH, and t-HPTH were 142 (IQR:110–240.3), 955 (IQR:1865–2448), 1394 (IQR: 949–2613) pg/ml respectively ($P<0.0001$). High PTH levels were associated with early SeS phase positivity ($P=0.024$) but not with late SeS phase positivity ($P=0.26$). There was no significant difference in preoperative levels of calcium on retention of SeS radiotracer on early and late phases ($P=0.545$). Correlative imaging with dual isotope was performed in 17 patients and ^{123}I uptake was positive in 88% of PA with RW.
Conclusion
Higher rates of RW were seen in p-HPTH followed by s-HPTH and t-HPTH and was dependent on PA size but neither on PTH nor calcium levels. Pre-operative PTH levels and size of the gland were major determinants of 99mTc-sestamibi positivity on early SeS phase whereas size is an independent predictor of late SeS phase positivity. SS scintigraphy might be a useful tool in suspected cases of RA.

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P183

Trabecular bone score in patients with active acromegaly

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Introduction
In previous studies, it was noted that increased serum growth hormone (GH) and insulin-like growth factor-1 (IGF-1) lead to the increased vertebral fractures risk in patients with acromegaly. This may be explained by the altered quality of bone rather than bone mineral density (BMD) loss. Trabecular bone score (TBS) is an easily available tool to obtain some surrogate information on bone micro-architecture from a routine DXA.
Objective
To evaluate trabecular bone score (TBS) and standard dual-energy X-ray absorptiometry (DXA) measurements in patients with acromegaly (compared to the healthy controls).

Methods
32 patients with confirmed active acromegaly and 35 healthy volunteers were enrolled into the study. Standard DXA with simultaneous calculation of TBS L1-L4 was performed using GE iDXA, TBS iNsight software v2.1 (Medimaps, Merignac, France). Serum insulin-like growth factor-1 (IGF-1) in patients with acromegaly was measured by the immunochemiluminescence assay, reference range (60–280 ng/ml).
Results
The groups were matched by sex (in total 21 men and 46 women) $P=0.657$; age 45.1 (95% CI 41.3–48.9) in patients with acromegaly and 44.7 (95% CI 42.7–46.7) $P=0.225$ and BMI 28.5 (95% CI 27.1–29.9) kg/m^2 in patients with acromegaly vs 26.7 (95% CI 25.3–28.1) kg/m^2 $P=0.065$. Mean IGF-1 level in patients with acromegaly was 703.79 ng/ml (95% CI 595.37–812.20). In patients with acromegaly there were not revealed significant differences in any DXA measurements compared to the control group: BMD L1-L4 1.162 g/sm^2 (95% CI 1.100–1.225) vs 1.221 g/sm^2 (95% CI 1.149–1.293); BMD T-score L1-L4 −0.28 s.d. (95% CI −0.79 to 0.23) vs 0.24 s.d. (95% CI −0.36 to 0.83); BMD Z-score L1-L4 −0.29 s.d. (95% CI −0.75 to 0.18) vs 0.12 s.d. (95% CI −0.40 to 0.63) ($P=0.221$, 0.192 and 0.245 respectively). TBS L1-L4 in patients with acromegaly was 1.408 (95% CI 1.358–1.458) vs 1.463 (95% CI 1.424–1.501) in controls ($P=0.080$). Statistically significant correlation between IGF-1 and TBS L1-L4 was not identified (as well as between IGF-1 and BMD, T- and Z-scores): $r=0.313$, 0.296, 0.274 and 0.092 respectively ($P=0.098$, 0.119, 0.150 and 0.635 respectively).
Conclusion
Acromegaly does not affect TBS or BMD in the value to be diagnostics in the individual subjects or in a small patient groups.
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Pituitary / Growth Hormone & IGF Axis

P184

Gut and bone connection: celiac disease presented as hypertrophic osteoarthropathy
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A 52-year-old postmenopausal woman was referred to endocrinology clinic for evaluation of persistent isolated elevation of alkaline phosphatase during routine check-up. Her past medical history was notable for hypothyroidism and vitamin D deficiency. She denied history of fractures or kidney stone. She denied using over the counter supplement, alcohol, smoking or drug use. Family history was suggestive of autoimmune disease, including celiac disease, type 1 diabetes, rheumatoid arthritis, and thyroid disease. Her physical examination was completely unremarkable. Initial laboratory investigation revealed elevated alkaline phosphatase (ALP) of 159 U/L (reference range: 40–150), with normal transaminase level. Subsequent labs were rechecked with further elevation of ALP to 177 U/L at 6 months and 212 U/L at 1-year follow-up. Additional labs revealed mild hypocalcemia with corrected calcium of 8.4, normal TSH, GGT, hepatitis B and C panel, ESR and CRP. Liver ultrasound revealed a 1.2 cm benign appearing hemangioma and no apparent culprit for abnormal enzymes. Further evaluation of persistent elevation of ALP revealed a fractionated bone alkaline phosphatase of 42.2 μg/L (reference range: 7–22.4 for postmenopausal woman). Subsequent nuclear bone scan demonstrated linear tram-like increased uptake in the bilateral tibia without focal areas of abnormal radiotracer uptake within the skeleton. Because of the patient's and family history of autoimmune disease as well bone scan finding, further work-up revealed a positive serum transglutaminase IgA indicated celiac disease. She was ultimately started on gluten-free diet with complete normalization of ALP. Periostosis is a radiographic hallmark of hypertrophic osteoarthropathy (HOA) which manifests along the shafts of tubular bones. HOA can also present as digital clubbing or synovial effusions. It is characterized by abnormal skin proliferation at the distal parts of the extremities as well as periosteal proliferation of the long bones. HOA is commonly associated with pulmonary disease but it could also be related to a variety of conditions involving different organ systems such as infection, inflammatory bowel disease, thyroid disease or hematologic malignancy. Herein, this case highlights HOA as a rare presentation of celiac disease.
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P185

The main bone mass predictors in healthy young and middle-aged men: lean mass and estradiol
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Introduction
Despite the high burden of osteoporotic fractures, bone evaluation in men is not without flaws, being frequently undervalued. We aimed at investigating the role of body composition, adipokines and classic bone determinants (sex hormones) as predictive factors for bone mass parameters in healthy young and middle-aged men.
Materials and methods
Anthropometric, bone mineral density (BMD) (assessed by Dual X-Ray Absorptiometry;DXA) and body composition parameters (assessed by DXA) and also the serum levels of C-terminal telopeptide of type I collagen (CTx), adipocytokines (leptin, resistin), total testosterone (free testosterone was calculated using mass action equations), total estradiol and sex hormone-binding globulin (SHBG) were determined from 30 healthy male volunteers aged 20-65 years old. Correlation analysis and also multivariable and hierarchical regression analyses were performed.
Results
BMD at various sites significantly correlated with body mass index (BMI), lean mass (LM), trunk fat mass, leptin, resistin, total estradiol and SHBG in the initial correlation analysis. When multiple regression analysis was performed, only LM and total estradiol remained independent significant predictors of BMD in men (together explaining 49% of whole-body BMD variance, $P<0.001$), while there were no independent predictors found for CTx. In the hirerchical regression analysis, the beta coefficient for BMI became non-significant when LM was added to the model.
Conclusions
LM and estradiol are the main BMD predictors in healthy young and middle-aged men. LM largely mediates the bone effects of the BMI. These parameters may find their place for fine tuning the male bone evaluation algorithms.
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P186

Teriparatide treatment in a patient with atypical femoral fractures associated with long-term bisphosphonate therapy
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Introduction
Bisphosphonates are the most commonly used drugs for the treatment of osteoporosis and have been shown to improve bone mineral density and reduce fractures. However, approximately a decade ago, atypical femoral shaft fractures were found to be a rare complication of bisphosphonate treatment. Atypical Femoral Fractures (AFF) represent fractures located between the lesser trochanter and the supracondylar flare of a femur. An increasing pool of evidence supports

their association with the prolonged use of bisphosphonates, even though a direct correlation has not been proven yet. In this report, we describe a patient who developed atypical femoral fractures after prolonged use of bisphosphonates.
Case
A 42-year-old man was referred to our out-patient clinic after operation for bilateral femoral fractures by orthopedists. The patient had the history of mild trauma. Her medical case history revealed that, for the past 6 years, he had received 70 mg/week alendronate as treatment for osteoporosis. Plain radiographs showed a transverse fracture in the bilateral femur, and cortical thickening was observed at the fracture site. His bone mineral densities (BMD) at the baseline dual-energy X-ray absorptiometry (DEXA) scan were as follows; femoral neck: 0.76 g/cm^2 (T score −1.2), femoral total: 0.79 g/cm^2 (T Score −1.6), and lumbar total: 0.70 g/cm^2(T Score −3.7). Blood tests indicated that his serum calcium, phosphate, and alkaline phosphatase levels were in the normal ranges. Any reason for secondary osteoporosis was not determined. The patient was diagnosed as bilateral atypical femoral fractures. The patient discontinued his alendronate regimen. The patient was treated with teriparatide 30 μg/day for osteoporosis for 18 months. After this treatment, lumbar total T-score was reduced to −2.9 (0.77 g/cm^2).
Conclusion
Bisphosphonates are one of the most widely prescribed drugs for the treatment osteoporosis and the reduction of fracture risk. In this report, we presented a patient with atypical fractures associated with long-term bisphosphonate treatment. The correlation between the long-term bisphosphonate use and atypical fractures has not been conclusively established. However, the drug holiday is suggested to reduce the risk of atypical fracture after prolonged bisphosphonates use. This case confirmed that teriparatide had a rapid bone anabolic effect on unhealed atypical fractures associated with chronic bisphosphonate use.

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P187

Detection of pulmonary metastases with 18F-Fluorocholine PET/CT and treatment of refractory hypercalcemia with denosumab in a patient with long term parathyroid carcinoma

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Introduction
Parathyroid carcinoma (PC) mediated hypercalcemia is often severe and more resistant to medical treatment. 18F-Fluorocholine PET/CT is a new technique used for determining the localization of parathyroid lesions. Denosumab, novel antiresorbtive agent, has been shown to have a useful role in hypercalcemia treatment. We report a male patient in long-term follow-up of PC who had refractory hypercalcemia due to pulmonary metastases revealed with 18-Fluorocholine PET/CT and who was successfully treated with denosumab.
Case
A 49-year-old man with recurrent PC initially presented in July 2007 with diffuse bone pain at lower extremities and hypercalcemia A neck ultrasound and CT scanning revealed a 3.9×3×3.5 cm solid lesion adjacent to the lower pole of the left thyroid lobe that was shown to represent a single hyperfunctioning parathyroid lesion on 99mTc-sestamibi (MIBI) parathyroid scintigraphy. The patient underwent a left parathyroidectomy along with en-bloc left thyroid lobectomy and left lateral lymph node dissection. Histological examination revealed parathyroid carcinoma. Due to postoperatively increased calcium and PTH levels, the patient was re-operated two times during the follow-up period for local recurrences. Afterwards, local radiotherapy was applied. One year later, laboratory investigations showed significantly raised calcium and PTH levels. Intravenous bisphosphonate as zolendronic acid 4 mg/28 days was started. For last 3 years, he did not take the medication due to social problems. He had admitted to our department with severe hypercalcemia 10 years later the initial operation at June 2017. He had hypercalcemia (16.8 mg/dl). He was screened for local recurrence or metastases. In 18F-FDG PET/CT diffuse nonhomogeneous hypermetabolism in medullary bones mostly associated with metabolic bone disesase was detected. His serum calcium levels were not decreased to <14 mg/dl levels with standard therapy such as aggressive saline rehydration, intravenous bisphosphonate, hemodialysis, oral cinacalcet. He had also acute pancreatitis in hospitalised period. For detection of local recurrence, 18-Fluorocholine PET/CT which revealed high uptake on pulmonary nodules was performed. Subcutaneous denosumab of 60 mg/28 days was given. After 3 doses of denosumab, total calcium was measured as 11.4 mg/dl.
Conclusion
As in this case, imaging with 18F-fluorocholine PET/CT is feasible in recurrent/metastatic parathyroid carcinoma. In our patient, 18F-fluorocholine PET/CT seems superior to FDG-PET/CT for detection of metastases. Denosumab is a good choice in treatment of hypercalcemia in patients who are resistant to other therapies such as hemodialysis, bisphosphonates and calcimimetics.

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P188

Bone mineral density decline following denosumab discontinuation might not be attenuated with previous bisphosphonate therapy

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Objective
Limited data suggest that the rebound increase in bone resorption and rapid bone mineral density (BMD) decline following sudden interruption of denosumab therapy can be avoided in patients previously treated with bisphosphonates. We aimed to compare BMD changes in osteoporotic patients after denosumab discontinuation regarding their previous bisphosphonate (BP) therapy.
Material and methods
There were 14 women (age 69 years, BMI 23.1 kg/m^2 on average) with postmenopausal osteoporosis who had been treated between 2011 and 2015 with denosumab for 2.8 (1–4) years at our outpatient clinic and were not prescribed with another antiresorptive after denosumab discontinuation. Before starting denosumab ten patients were on BP therapy, while the others were treatment naïve. One patient had a history of multiple vertebral fractures and two patients had sustained nonvertebral fractures. There were no fractures during denosumab therapy. BMD was measured at lumbar spine (LS), total hip (TH) and femoral neck (FN) by DXA when denosumab was stopped and 12 to 18 months later. The data were analyzed using exact nonparametric tests.
Results
At the time of denosumab discontinuation 5 patients (36%) were vitamin D sufficient (25OH vitamin D > 75 nmol/l). BMD decreased on average statistically significantly at all sites, (marginally at LS and most clearly at FN). There were no statistically significant differences in average BMD decrease with respect to previous BP therapy. However, there was statistically significantly lower decrease at LS on average among the vitamin D sufficient patients. Off denosumab, one treatment naïve patient and one former BP user sustained five and four vertebral fractures, respectively. Fractures were confirmed with MRI and occurred approximately 13 months after last denosumab dose. The estimated proportion of patients with fractures (adjusted Wald method) was 19% (95% CI 3–41%).
Conclusion
After stopping denosumab BMD similarly decreased in all patients, regardless of previous BP use.

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P189

Novel heterozygous mutation of tissue-non-specific alkaline phosphatase (TNSALP) gene causing late-onset hypophosphatasia

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Background
Hypophosphatasia (HPP) is a rare metabolic, inherited disease of bone metabolism, caused by loss-of-function mutations within the gene coding for TNSALP, that result in a decrease in serum ALP concentrations and consequent accumulation of ALP substrates outside of the cell, including inorganic pyrophosphate which inhibits bone mineralization. HPP leads to a variety of clinical manifestations across all ages and its prognosis is conditioned principally by the skeletal complications, which generally reflect patient age at presentation.
Case report
We report the case of a 60-year-old woman presenting with chronic kidney disease stage 4 due to progressive nephrocalcinosis and recurrent renal calculi. Starting from the age of 37 yr, when a fracture of distal ulna occurred, the patient had experienced multiple fractures, including bilateral atypical subtrochanteric femoral fractures, and increasing pain, which had resulted in a decrease in her mobility from fully mobile to bed-bound. On physical examination the patient was 145 cm tall and weighed 45 kg. Examination of the lungs, heart and abdomen was unremarkable. ECG and EGA were normal. An ultrasonographic study of abdomen revealed kidneys reduced in volume with irregular profile; bilaterally absent hydronephrosi. Chest radiographs showed severe sclerosis with marked dysmorphism of the scapulae, the humerus and the clavicles. Laboratory evaluation revealed low serum ALP levels (11 UI/l; n.v. 40–150) and high values of Vitamin B6 (33.5 μg/dl; n.v.8.7–27.2), consistently with a diagnosis of HHP. Serum PTH was high (94.20 pg/ml; n.v. 8–76) and 25OH-vitamin D low (9.9 μg/dl; n.v. >30), with total calcium 10.2 mg/dl. Mutation analysis revealed a novel heterozygous mutation in the TNSALP gene (c.1415A$>$G, p.His472Arg). The mutation identified in this patient's TNSALP gene have never been previously identified as causing HPP.
Conclusion
We report a novel missense mutation of TNSALP gene, causing late-onset HHP. Up to date over 300 mutations have been identified, which result in a variable loss of function in the enzyme and a consequent decrease in serum ALP concentrations. A clear correlation genotype-phenotype has not been recognized yet.

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P190

Orthopedic patient with hearing impairment and dizziness due to the undiagnosed Paget's disease of bone

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A 67-year-old female patient with a more than five-year history of symptomatic treatment of bilateral hip joint arthrosis, lumbar spine spondiloarthrosis as well as progressive hearing impairmen and dizziness was referrred by orthopedic surgeon to the endocrinology ward for diagnostic workup of metabolic bone disease. From the family history it was known that her mother had similar complains by the age of 60, which rapidly led to disability to walk, but she was never properly investigated. Patients plasma calcium (2.24 mmol/l) and phosphorus (1.48 mmol/l) were within the normal range, but parathyroid hormone (1294 U/l, 12.2 pmol/l) and alkaline phosphatase (1294 U/l) were significantly elevated. The skull radiography revealed areas of increased density and fibrous cortical layer, and similar changes were observed in left thigh and pelvic bones, both hip joint surfaces were narrowed, sclerotic and thickened. The skull CT scan indicated that the cause of the bilateral sensoneural hearing loss was a diffuse and uneven hyperostosis leading to compression of the auditory nerves. Magnetic resonance imaging of lumbosacral, lower thoracic vertebrae revealed degenerative spondylarthrosis. All these findings indicated that patient had the Paget's bone disease. Patient received a high dose vitamin D therapy followed by a single 5-mg dose of intra venous zoledronate injection and long term calcium and vitamin D substitution that led to an increase of the bone mineral density. After 6 months the knee joint replacement with endoprosthesis was performed.
Discussion
Our case report is showing importance of measurement of the alkaline phosphatase within the endocrinological investigation for metabolic bone disease in patients complaining of hearing loss, vertigo and osteoarthritis. Paget's disease of bone is a chronic disorder of bone remodelling that begins with excessive bone resorption followed by an increase in bone formation. Mostly it manifests in the 5th decade of life and diagnosed in the sixth decade. Disease commonly affects the pelvis and spine, the sacrum, the skull, and the femur. Skull involvement results in headaches, impaired hearing, vertigo and tinnitus.

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P191

Tumor-induced osteomalacia associated with mesenchymal tumor: a challenging case report

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Introduction
Tumor-induced osteomalacia (TIO) or oncogenic hypophosphatemic osteomalacia (OHO) is a rare paraneoplastic syndrome characterized by renal phosphate wasting leading to hypophosphatemia and secondary osteomalacia. TIO was first described in 1947 by Robert McCance and only 500 of cases have been reported in literature since then, approximately 200 of cases during this decade.
Case report
In 2014, a 32-year-old female presented with waist pain, myalgia, muscle weakness. The patient felt unhealthy after second childbirth. In June 2015 MRI scan revealed bilateral acute sacroiliitis. Treatment with sulphasalazine, methylprednisolone, methotrexate and later with etanercept was started, but was ineffective. In May 2016 repeated MRI showed bilateral avascular femoral head necrosis of unknown origin. Plain radiography showed osteoporosis at thoracic, lumbar vertebrae, hip bone and femur, fracture of superior ramus of pubis, compressive fractures in Th8-Th9. Dual energy x ray absorptiometry (DXA) scans confirmed low bone mineral density at the spine 0.516 g/cm^2 (Z-score -4.8), hip neck 0.507 g/cm^2 (Z-score -2.9) and hip total 0.496 g/cm^2 (Z-score -3.6). Other causes of secondary osteoporosis were excluded and the antiosteoporotic treatment with denosumab was started. The patient was first seen by an endocrinologist in October 2016 because of progressing symptoms. Biochemical evaluation revealed hypophosphatemia 0.3 mmol/l (n: 0.78–0.153) and low 24-h urine phosphorus excretion 8.78 mmol/24 h (n: 12.9–42.0). Hypophosphatemia was treated with phosphate supplements but where was no improvement. In September 2017 patient noticed a soft lump in the right groin. Right leg ultrasound and MRI revealed $1.5\times1.8\times2.0$ cm size tumor between sartorius and adductor longus muscles. Whole-body MRI and bone scintigraphy showed no metastasis or other tumors. In October 2017 the whole-body scintigraphy with somatostatin analogues 99mTC-tektrotyd showed intensive uptake of radiotracer at the tumor. Tumor biopsy was performed and the result confirmed giant cell tumor of soft tissue (GCT-ST). FGF-23 values were found increased eightfold and being 867 U/l (n: 26–110). With strong prediction of TIO, in January 2018 the patient underwent tumor removal surgery. One week after surgery serum phosphate reached normal range. Histopathology examination is still in process.
Conclusion
A stepwise approach to tumor localization with functional and anatomic imaging for the diagnosing TIO is essential. Patients should first be assessed with a thorough physical examination. Removal of the tumor successfully cures this debilitating disease.

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P192

Osteoprotegerin and bone metabolism markers in postmenopausal women with primary hyperparathyroidism

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Objective
To study relationship between osteoprotegerin (OPG) and bone metabolism markers in postmenopausal women with primary hyperparathyroidism (PHPT) compared postmenopausal women without PHPT.
Materials and methods
We studied 30 postmenopausal women with PHPT, average age 62.5 ± 6.12. The control group were 16 postmenopausal women without PHPT, mean age 59.7 ± 6.28 in physiological menopause. We analyzed anthropometric data and history of fractures. Examination: total calcium, Ca^{++}, phosphorus, albumin, creatinine, alkaline phosphatase, PTG, OPG, crosslaps, osteocalcin.
Results
The were no differences in the age ($U=138.5$, $P=0.052$), height, m ($U=216.5$, $P=0.99$), weight, kg ($U=202.5$, $P=0.72$), BMI kg/m^2 ($U=196.5$, $P=0.61$), duration of menopause, years ($U=146.5$, $P=0.08$). Calcium total was 2.75 (2.69-2.82) mmol/l in postmenopausal women with PHPT vs 2.44 (2.31-2.50) mmol/l in the control group, $U=4$, $P=0.001$; Ca^{++}1.27 (1.26-1.36) mmol/l vs 1.04 (0.98-1.14) mmol/l in the control group, $U=4.24$, $P<0.0001$; phosphorus 0.94 (0.80-1.06) mmol/l vs 1.36 (1.32-1.40) mmol/l in the control group, $U=0.001$, $P=0.029$; alkaline phosphatase 122.0 (89.0-146.0) mmol/l vs 84.0 (72.0-84.0) mmol/l in the control group, $U=4.0$, $P=0.126$; PTG 111,1 (88.5-144.3) pg/ml vs 54.7 (35.4-55.3) pg/ml, $U=0.001$, $P<0.0001$; osteocalcin 32.33 (21.95-40.33) ng/ml vs 19.9 (16.0-27.8) ng/ml, $U=23$, $P=0.07$; crosslaps 0.60 (0.37-0.79) vs 0.46 (0.33-0.54), $U=16$, $P=0.2$. Significant differences were detected in calcium total, Ca^{++}, phosphorus, PTG in postmenopausal women with PHPT compared control group, there were no differences in alkaline phosphatase, osteocalcin, crosslaps. We detected negative correlation between OPG level and calcium total $r_s=-0.6$, $P<0.05$, $r_s=-0.7$, $P<0.05$, PTG $r_s=-0.6$, $P<0.05$.
Conclusion
The results of the study confirmed high bone metabolism in postmenopausal women with PHPT compared control group. The results may indicate association between PTG, calcium level and OPG.

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P193

Endocrine osteoporosis characteristics (about 177 cases)

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Background
Osteoporosis is a not uncommon complication of endocrine disease. It may even be accompanied by endocrinopathy. The aim of study was to determine mineral bone density profile of patients with endocrinopathy and define the osteoporosis and osteopenia prevalence in these patients.
Materials and methods
Descriptive study included 177 patients followed for endocrinopathy (hypercorticism, hyperparathyroidism, prolactinoma and hypogonadism) in Endocrinology and Diabetology department of Ibn Rochd University Hospital of Casablanca, from 2011 to 2017. Each patient had a phosphocalcic balance, a vitamin D test and bone densitometry. Several variables were studied such as age, gender, fracture antecedant. Statistical analysis performed by the software SPSS.16.
Results
Mean age of our patients was 38 (16-73) years, with a female predominance (sex ratio: 0.3). The etiologies were represented by hyperparathyroidismin 65 patients, hypercorticismin 61 patients, prolactinoma in 12 patients and hypogonadism in 39 patients. An abnormal bone density was found in 85% of patients. Osteoporosis prevalence was 68% with predominance of the spine localization during hypercoticism (45%) and hypogonadism (38%) with an average T-score of -1.98 ± 1 among patients with hyperparathyroidism. Osteoporosis predominated in the forearm in 35% of patients. Osteopenia was found in 37% of patients with femoral predominance. Vitamin D deficiency was found in 74% of our patients. These bone density abnormalities were revealed by endocrine pathology in 75% of patients, 18% of whom were at the stage of complications such as bone fractures.
Conclusion
This work shows a high incidence of osteoporosis and osteopenia in patients treated for endocrine diseases especially who followed for hypercorticism and hypogonadism 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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Pituitary Basic

P194

Osteoprotegerin and distal radius bone mineral density in postmenopausal women with primary hyperparathyroidism

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Objective
To study relationship osteoprotegerin (OPG) and distal radius bone mineral density (BMD) in postmenopausal women with primary hyperparathyroidism (PHPT) compared postmenopausal women without PHPT.
Materials and methods
We studied 30 postmenopausal women with PHPT, average age 62.5 ± 6.12. The control group were 16 postmenopausal women without PHPT, mean age 59.7 ± 6.28 in physiological menopause. We analyzed anthropometric data and history of fractures. Examination: total calcium, phosphorus, albumin, creatinine, PTG, OPG, vitamin D, BMD measurements in the lumbar spine, femoral neck, total hip, and distal 1/3 radius by DXA (T-score$_{33\%}$, BMD$_{33\%}$ g/cm^2).
Results
The were no differences in the age (U = 138.5, $P=0.052$), height, m (U = 216.5, $P=0.99$), weight, kg (U = 202.5, $P=0.72$), BMI kg/m^2 (U = 196.5, $P=0.61$), duration of menopause in both group, years (U = 146.5, $P=0.08$). Osteoporosis of distal 1/3 radius was founded in 33% (10 cases), osteopenia in 43% (13 cases) in postmenopausal women with PHPT(T-score$_{33\%}$ = –2.3 (–3.2 –1.5, BMD$_{33\%}$ = 0.67 (0.59–0.75) g/cm^2), and low distal radius BMD was no founded in the control group (T-score$_{33\%}$ = −0.3 (−0.7 –0), BMD$_{33\%}$ = 0.87 (0.82–0.9) g/cm^2). Significant differences was detected in the distal radius BMD in postmenopausal women with PHPT compared postmenopausal women without PHPT ($U_{\text{T-score33\%}}=22.0$, $P<0.0001$, $U_{\text{BMD33\%}}=20.5$, $P<0.0001$). We detected correlation between OPG level and distal radius BMD: $r_{\text{sT-score33\%}}=0.7$, $P<0.05$, $r^2_{\text{s33\%g/cm}}=0.64$, $P<0.05$.
Conclusion
The results of the study confirmed reduced BMD in cortical bone, particularly at the distal radius, in postmenopausal women with PHPT compared control group. The results may indicate association between OPG level and low distal radius BMD.

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P195

Cystic fibrosis-related bone disease in young adults affected with cystic fibrosis awaiting lung transplantation for end-stage respiratory failure

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Background
Cystic fibrosis-related bone disease (CFBD) is an emerging complication of cystic fibrosis (CF), especially in CF-lung transplant candidates for end-stage disease.

Objectives
The assessment of vitamin D levels, bone mineral density (BMD) and morphometric and clinical prevalent fragility fractures in a cohort of young adults affected with CF awaiting lung transplantation for end-stage respiratory failure.
Methods
In 42 CF-patients (24 females, age 33.7 ± 8.3 years), who were consecutively referred as lung transplant candidates to our Hospital, we evaluated the parameters of calcium metabolism, including 25-OH vitamin D (25OHVitD) levels, BMD by dual-energy x-ray absorptiometry and vertebral fractures by spinal radiograph.
Results
Mean 25OHVitD levels (22.0 ± 10.4 ng/mL) were below the reference range and hypovitaminosis D (25OHVitD <30 ng/mL) was found in 34 patients (81%) despite vitamin D supplementation in the majority of patients. Even mean daily calcium intakes (615.5 ± 266.8 mg/day) were lower than that recommended (1000 mg/day). BMD FT Z-scores were inversely correlated with prednisone cumulative exposure ($r=-0.383$, $P=0.015$) and BMD FN and FT Z-scores were directly correlated with albumin-adjusted calcium ($r=0.387$, $P=0.020$ and $r=0.346$, $P=0.039$ respectively) and 25OHVitD levels ($r=0.508$, $P=0.001$ and $r=0.554$, $P=0.0001$ respectively). In particular, no patients with normal 25OHVitD levels showed FT Z-scores <-1.0. A BMD below the expected range for age (Z-score <-2.0) was found in 22 patients (52.4%) and at least one prevalent fracture in 18 patients (45.2%). In patients with a BMD Z-score <-2.0 the prevalence of fragility fractures tended to be higher (59.1%) than in patients with a BMD within the range of age (30.0%, $P=0.059$), whereas these two groups were comparable as far as age, gender, body mass index, familiar history of fracture, glucocorticoid exposure, daily calcium intake and vitamin D supplementation, prevalence of main CF-related comorbidities, albumin-adjusted calcium and 25OHVitD levels.
Conclusions
Despite the improvement of CF-care, CFBD is still highly prevalent in young adults awaiting lung transplantation for end-stage CF. In order to optimize bone health of CF population approaching lung transplantation, glucocorticoid use should be minimized whenever possible, optimal calcium intake ensured and hypovitaminosis D adequately corrected.

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P196

Recurrent vertebral fracture after denosumab discontinuation in a male patient with severe osteoporosis

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Introduction
Discontinuation of denosumab may rarely lead to rebound fractures, although the evidence is low, since available data have derived from case reports and post-hoc analyses.
Case presentation
A 45-year old Caucasian male was presented at the outpatient clinic in February 2016 for evaluation and management of severe osteoporosis, which had been complicated with multiple vertebral low energy fractures at the 10 th to 12th thoracic vertebrae (T10-T12) and at the 1st (L1), 2nd (L2), 4th (L4) and 5th lumbar vertebrae (L5). These fractures were diagnosed in 2013 after continuous back pain following a mild injury and weight-bearing activities. Severe osteoporosis was diagnosed and the patient was initially treated with teriparatide (for 24 months) showing significant improvement in physical activity. Bone mineral density (BMD) values after teriparatide treatment were 0.861 mg/cm^2 (T-score: –3, Z-score: –2.5) for lumbar spine, 0.78 mg/cm^2 (T-score: –2.2, Z-score: –1.4) for neck and 0.783 mg/cm^2 (T-score –2.4. Z-score: –1.7) for total hip. Evaluation for causes of secondary osteoporosis was negative. He was also receiving calcium supplementation (1000 mg/d) and cholecalciferol 800 IU/d (25-hydroxy-vitamin D concentrations: 29 ng/ml). After three injections of denosumab (March 2017), the patient's lumbar spinre BMD increased to 0.882 mg/cm^2 (T-score: –2.8, Z-score: –2.2). However, he was complaining of continuous musculoskeletal pain since denosumab injections and he omitted the fourth one. The patient attended the outpatient clinic in September 2017 complaining of a new severe back pain after mild physical activity. Spine magnetic resonance imaging (MRI) revealed a new vertebral fracture in L4 and concomitant biconcave deformation of T11 and T12. After excluding other causes of low bone mass, denosumab was re-initiated.
Conclusions
This is the first case of a male patient having sustained a new vertebral fracture, nine months after his last denosumab dose. The possibility of a rebound fracture, although low, should always be taken under consideration after denosumab discontinuation, especially in patients at high fracture risk, not previously being treated with bisphosphonates.

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P197

Microindentation in the study of bone properties for type 1 diabetes mellitus patients

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Background and aims
Patients with T1D present some predisposing factors to fractures. The aim of the present study is to analyse the bone tissue quality in T1DM women and healthy controls by bone microindentation, as well as their relationship with bone mineral density (BMD).
Materials and methods
Cross-sectional study including 45 women with T1D at least with one year of duration and 21 healthy controls adjusted by age and BMI. Women with osteoporosis or previous pathologic fractures, presence of diseases that predispose to the development of osteoporosis, and patients who did not consent to participate in the study were excluded. Anthropometric variables were collected using standardized methods. T1DM-related variables were collected. NCEP-ATP III modified criteria was used to define metabolic syndrome (MetS). A blood analysis was performed in all subjects, including fasting glucose, lipid profile, calcidiol, calcium and iPTH. In T1DM patients, glycated hemoglobin and albumin/creatinine ratio was also determined. BMD was measured in lumbar column, femoral neck and total femur in all subjects by dual energy x-ray absorptiometry. BMS was obtained by microindentation technique.
Results
No differences between T1D patients and healthy controls were observed in BMS, BMD nor in calcium, iPTH or calcidiol (Table 1). Among T1D patients, mean HbA1c was 7.52% + 1.0 and mean time since diagnosis was 22.6 + 12.2 years. 8 patients (17.7%) met the MetS criteria, and in 12 patients (26.7%) microvascular complications were present. A trend towards a lower BMS was observed in parallel to an increase of the number of Metabolic Syndrome criteria (79.2 + 8.5 vs 75.1 + 7.9, P 0.273, 1 vs3 or more MetS criteria, respectively) and in patients with microangiopathy (78.3 + 10.8 vs 80.5 + 7.6, P 0.447, in patients with and without microangiopathy, respectively).
Conclusion
T1DM women show bone tissue properties comparable to controls. Microangiopahy and MetS seems to affect negatively to BMS.

Table 1

Characteristic	Control	T1D	P
n	21	45	
Age (y)	38.4 + 9.9	39.3 + 10.3	0.729
BMI (Kg/m^2)	24.7 + 4.5	25.3 + 4.9	0.617
T-score, lumbar	−0.10 + 1.2	−0.50 + 1.1	0.296
T-score femoral neck	−0.5 + 0.9	−0.67 + 1.0	0.624
BMS	80.3 + 7.1	79.9 + 8.5	0.825
Calcium (mg/dL)	9.54 + 0.3	9.61 + 0.4	0.653
iPTH (pg/mL)	36.2 + 14.6	44.3 + 28.1	0.542
Calcidiol (ng/mL)	26.0 + 11.4	25.2 + 11.9	0.818

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Relationships between hormonal parameters, body fat distribution and bone mineral density in women with menstrual disorders

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Available evidence suggests that unfavorable changes in the distribution of body fat resulting from hormonal imbalance associated with ovarian insufficiency may exert detrimental effects on bone mineral density (BMD). The aim of this study was to verify if densitometrically determined volumes of visceral (VAT), female (FAT) and android (AAT) adipose tissue influence BMD in women with menstrual disorders, and if these relationships are modulated by endocrine factors. The study included 293 Caucasian women (mean age 26.7 ± 4.4 years) with at least 6-month history of secondary amenorrhea. Volume of fat in all analyzed regions correlated positively with BMD in lumbar spine (VAT: $R = 0.277$, FAT: $R = 0.345$, AAT: $R = 0.336$) and entire skeleton (VAT: $R = 0.453$, FAT: $R = 0.527$, AAT: $R = 0.529$). Moreover, BMD in the lumbar spine and entire skeleton correlated positively with body mass index ($R = 0.380$ and $R = 0.599$, respectively) and free androgen index values ($R = 0.150$ and $R = 0.279$), and showed inverse correlations with sex hormone-binding globulin ($R = -0.191$ and $R = -0.326$). None of the above mentioned parameters turned out to be an independent predictor of BMD. These findings imply that distribution of adipose tissue is only one of many determinants of BMD in women with ovarian insufficiency and therefore, should not be considered as a single risk marker for bone mass deficiency. Due to their specific metabolic and hormonal profile, physiological functional differences between subcutaneous and visceral adipose tissue in women with menstrual disorders seem to be blurred. As a result, determination of body fat distribution in patients with ovarian insufficiency is probably of lesser clinical importance.

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Long term follow up of patients with hypophosphatemic rickets in a Public Institution in Brazil

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Introduction
Hypophosphatemic rickets comprehends a group of hereditary diseases characterized by hypophosphatemia and defective bone mineralization. The most common form is X-linked, with a prevalence of 1:20.000.
Objectives
Describe the follow up of patients with hypophosphatemic rickets in a public center in Brazil.
Methods
Patients with hypophosphatemic rickets were selected from a database of Endocrinology and Metabolism Service of Paraná (SEMPR). Medical records were revised to collect clinical and laboratory evaluation.
Results
Twenty-two patients were included, being 15 women. The median follow up was 11 years (1 month – 27 years), with a median age at diagnosis of 105 months (13 – 384 months). All patients presented with bone deformity, 11 (50%) patients with genus varus, 10 (45%) patients with genus valgus and 1 (4%) patient with both. Other bone deformities present were: 6 (27%) lordosis, 6 (27%) scoliosis, 5 (22%) bone deformity with frontal bossing and 12 (54%) epiphyseal enlargement. Median initial laboratory results were as follows: calcium 9.1 mg/dL (8.3–9.9 mg/dL), phosphorus 2.18 mg/dL (1.3–3.0 mg/dL), alkaline phosphatase 848 U/L (19.26–2109 U/L), parathormone 122 pg/mL (6–523 pg/ml), total reabsorption of phosphorus of 43%. Initial X-rays showed 12 (54%) patients with typical rickets findings, 3 (13%) patients with reduced bone mineral density and 2 (9%) patients with fractures. Fanconi syndrome was diagnosed in 5 (22%) patients. Treatment consisted of phosphorus supplementation in 14 (63%) patients with a median dose of 1.7 gr/day, calcitriol in 13 (59%) with a median dose of 0.32 mcg/day and combined treatment in 9 (40%). During follow up showed fractures in 8 (36%) patients, most frequently in femur (7) 41% and tibia (4) 23%. Eight patients were evaluated DEXA and all of them showed increased BMD in all sites. Nine patients were evaluated with hand x-ray for bone age and all showed with delay, with a median of 19 months (12-84 months). Alkaline phosphatase after treatment went down to a median of 236 U/L (decrease of 72%) and creatinine went up by a median of 37%. Calcium, phosphorus and parathormone didn't show significant alterations. Kidneys were assessed by ultrasonography in 17 (77%) patients, and showed nephrocalcinosis and nephrolithiasis in 3 (17%) and renal parenchymal disease in 4 (23%). Secondary hyperparathyroidism was observed in 1 (4%) patient.
Conclusion
Phosphorus and calcitriol induced bone mineralization leading to symptom improvement and increased bone mineral density. Then, overtreatment could possibly lead to renal complications, as shown in 40% of patients.

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P200

Genetic polymorphisms may modulate bone and energy metabolism of mountain cycling ultramarathon athlete's

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Introduction
The interaction between bone and energy metabolism may be enhanced in high demanding physical activities. We hypothesize that genetic background may modulate the exercise-associated bone and energy responses of athletes participating of a mountain cycling ultramarathon.
Methods
Fifty-five non-professional athletes (mean age 44.8 ± 7.1 years) participating in a 9-day mountain cycling ultramarathon (TransPortugal) were evaluated. Before and immediately after the race were determined the following parameters: insulin, glucose, uric acid and creatinine by standard methods; IL-6-plasma and carboxyglutamic acid residues of osteocalcin (Gla-OC)-plasma by ELISAs. The genetic polymorphisms of leptin-*LEP-rs1137101,* βeta-2 adrenergic receptor-*ADRβ2-rs1042713,* Osteocalcin-*BGLAP-2274911* were determined by PCR-RFLP. Δ% represents values adjusted for plasma volume. Body composition was evaluated by BIA-Quantum-X. Participants were also categorized according to the number of courses completed (<9 or 9 courses).
Results
The genotype's frequencies of polymorphisms analyzed were: *LEP* (homozygous G 0.29, heterozygous 0.51, homozygous A 0.20), *ADRB2* (homozygous Gli 0.51, heterozygous 0.25, homozygous Arg 0.07) and *BGLAP* (homozygous T 0.60, heterozygous 0.31, homozygote C 0.09). The athletes with *LEP* polymorphism AA + AG genotypes (*versus* GG) had a favorable predisposition to: complete 9 courses, adjusting for age, gender, average speed, % fat mass and waist circumference (OR = 5.0 [1.1–22.5], $P = 0.036$) and to finish the race faster, adjusting for age, fat mass percentage in the pre-test, pre-run waist circumference and all stages (OR = 8.0 [1.1–61.1], $P = 0.044$). For this model, the *LEP*-A carriers presented higher Δ% uric acid ($P = 0.041$) and Δ% Gla-OC ($P = 0.037$). In 9-courses completers, *LEP*-A carriers presented a gain increase in Δ% IL-6 ($P = 0.012$). For the *ADRB2* polymorphism, athletes with AG + GG genotypes

(*versus* AA) presented lower levels of post-race: insulin, HOMA-IR and HOMA-B ($P<0.05$). For *BGLAP* polymorphism, athletes with CC+CT genotypes (*versus* TT) had higher post-race levels and Δ% of HOMA-IR and HOMA-B ($P<0.05$). Covariance analysis showed a significant effect of *LEP*-A carriers on Δ% glucose ($F=4.712$, $P=0.036$), controlling for Δ% Gla-OC, Δ% IL-6, age, average speed and completers. Other covariance analysis showed significant effect of basal skeletal muscle mass on the Δ% Gla-OC ($F=4.650$, $P=0.037$), controlling for Δ% uric acid, creatinine, glucose, age, average speed and completers.

Conclusion

The *LEP*, *ADRβ2* and *BGLAP* polymorphisms, related to bone and energy metabolism, may modulate the performance of athletes. This work supports a hypothesis of the influence of a co-modulatory action between genetic factors and mediators released during long-term exercises.

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May polymorphisms of DHFR, CBS and MTHFR genes modulate metabolic and bone remodeling parameters associated with reduced bone mineral density?

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Objectives

To study the association of functional polymorphisms at DHFR, CBS and MTHFR genes with bone mineral density (BMD) and metabolic parameters of bone remodeling.

Materials and methods

BMD (g/cm2) was measured by DEXA in 391 subjects: 174 with normal BMD (137F 37M; age=48.79±12.99 years; BMI=29.61±5.22 kg/m2), 62 with osteopenia (48F 14M; age=56.06±12.96 years; BMI=27.64±4.94 kg/m2) and 154 with osteoporosis (119F, 35M; age=64.17±11.04 years; BMI=27.48±4.56 kg/m2). Metabolic bone remodeling parameters were analyzed: LDL, HDL, total cholesterol, triglycerides, HOMA, parathormone (PTH), alkaline phosphatase (AP), bone fraction of alkaline phosphatase (AP_BF) and osteocalcin. Genetic polymorphisms were evaluated by PCR and PCR-RFLP. Statistical analysis by SPSS 23.0. Statistical significance for $P<0.05$.

Results

The three studied groups differ in age and BMI being those with osteoporosis the oldest and with the lower BMI. Individuals with reduced BMD (osteopenia and osteoporosis) showed higher PTH and osteocalcin. Those with osteoporosis also showed higher AP. Individuals with allele C of MTHFR_C677T polymorphism (CC or CT) showed a 2.194 risk for the development of reduced BMD ($P=0.024$; OR=2.194; CI95% [1.109–4.342]) when adjusted for age and BMI. For the studied polymorphisms at DHFR and CBS genes we did not find association with the susceptibility for osteopenia or osteoporosis. When we compared metabolic bone remodeling parameters within genotypes of the studied polymorphisms, we found: For DHFR we did not find statistical differences when we included the all studied population. Although, we found lower AP, AP_BF and total cholesterol for DHFR_ins/ins genotype in normal BMD individuals. For CBS we did not find statistical differences when we included the all studied population. Although, we found lower AP and AP_BF for CBS_-/- genotype in osteoporotic individuals. For MTHFR we found higher AP and AP_BF and lower HDL for CC individuals, and higher osteocalcin for Individuals with allele C (CC or CT) when we included the all studied population. When we separated individuals according to their BMD, we found lower HDL and total cholesterol and higher osteocalcin for osteoporotic individuals carrying allele C (CC or CT).

Conclusion

MTHFR_C677T polymorphism seems to confer susceptibility for reduced bone mass, either directly or by modulating metabolic bone remodeling parameters. On the other hand, genetic polymorphisms of DHFR and CBS seem to play and important role in modulating metabolic bone remodeling parameters associated with reduced bone mineral density.

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Calcium & Vitamin D metabolism

P202

Vitamin D levels in two ethnic groups of patients with diabetes

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Introduction

- Vitamin D deficiency is thought to impair insulin action and glucose metabolism.
- Migrants who live in Western countries seem to have lower 25(OH)VitD levels, not only from their white counterparts but also from their native populations in their country of origin.

Objectives

- We investigated a cohort of predominantly white Greek Caucasian and Bangladeshi immigrant patients with diabetes mellitus in order assess the differences in 25(OH)VitD.

Methods

- A total of 165 patients from Bangladesh and 118 patients from Greece with diabetes were assessed for diabetes and 25(OH)VitD status.
- All measurements of 25(OH)VitD were categorized into two halves of the year: the first period from mid-October until mid-April: winter period; and second period from mid-April until mid-October: summer period.
- The prevalence of vitamin deficiency (<20 ng/ml), insufficiency (20-<30 ng/ml) and sufficiency (≥30 ng/ml) was estimated.

Results

- A total of 76 Bangladeshi patients (65 men and 11 women) and 43 (36 men and 7 women) Greek patients were recruited over the winter period and 83 (80 men and 3 women) Bangleshi patients and 71 (61 men and 10 women) Greek patients over the summer period.
- Patients from Bangladesh were younger than Greek patients (43.96±8.1 vs. 48.78±9.3 years old).
- Patients from Bangladesh had slightly worse glycemic control as compared with Greek patients (HbA1c=7.76±1.5% vs. 7.57±1.7%, $P=0.3$).
- The 25(OH)VitD levels of Bangladeshi patients were significant lower compared to Greek patients (12.42±5.86 vs. 23.06±12.36, $P<0.001$).
- The same pattern also occurred regarding the seasonal periods. In Bangladeshi patients, the mean level of 25(OH)VitD in winter and summer periods was 11.28±5.53 and 13.68±6.04 ng/ml, respectively. In Greek patients the mean level of 25(OH)VitD in winter and summer periods was 21.97±13.18 and 24.19±12.32 ng/ml, respectively.
- The prevalence of 25(OH)VitD deficiency, insufficiency and sufficiency differ significantly in two groups of patients and in Bangladeshi patients was 90.0%, 8.6% and 1.2%, respectively, while in Greek patients, the rates were 43.2, 32.2 and 24.57%, respectively.

Conclusions

- The prevalence of vitamin D deficiency is very high amongst patients with diabetes but immigrants are at greater risk. Vitamin D supplementation could be valuable mostly during the winter period for patients with diabetes.

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P203

Effects of steroid hormone on Calbindin-D_{9k} expression in rat cerebellum

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Introduction
Calbindin-D_{9k} is a 9 kDa polypeptide expressed in the mammalian intestine, uterus, and pituitary gland. Calbindin-D_{9k} increase Ca^{2+} absorption by buffering intracellular Ca^{2+}. The intracellular concentration of calcium is regulated by calcium related proteins such as calbindin-D_{9k}, TRPV1 and PMCA1. The regulatory effect of steroid hormones and glucocorticoids on calbindin-D_{9k}, TRPV1 and PMCA1 expressions in the cerebellum are currently unknown. In this study, we investigate the expressions of calbindin-D_{9k}, TRPV1 and PMCA1 by sex steroid hormones and glucocorticoids in rat cerebellum.
Methods
To investigate the effect of sex steroid hormones and glucocorticoids to the cerebellum calbindin-D_{9k}, TRPV1 and PMCA1 expressions, 14 days old rat were administered 40 ug/kg of E2, 20 mg/kg of P4, 10 mg/kg of ICI 182,780 and 13 weeks old rat were administered 10 mg/kg of Dexamethasone (Dex), 50 mg/kg of RU486.
Results
Transcriptional level and localization of Calbindin-D_{9k}, TRPV1, PMCA1 were examined in the cerebellum. mRNA and protein level of Calbindin-D_{9k} was increased by Dex, but not by E2 nor P4. Immunofluorescence shows that calbindin-D_{9k} were mainly localized in the purkinje cell. Like the expression of calbindin-D_{9k}, mRNA levels of TRPV1 and PMCA1 only increased in response to Dex treatment.
Conclusion
These results are correlated with calbindin-D_{9k}, TRPV1 and PMCA1 expressions were regulated by glucocorticoids in cerebellum. Especially, the localization and regulation of calbindin-D9k in purkinje cell could indicate that glucocorticoids can bring functional changes in the purkinje cell.

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P204

Effects of glucocorticoid on mucin secretion by calcium-related proteins in mouse lung

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Calcium is important for physiological functioning in many tissues and is essential in mucus secretion and muscle contraction. Intracellular concentrations of calcium are regulated by calcium-related proteins such as TRPV4, TRPV6, CaBP-9k, NCX1, and PMCA1. In this study, the relationship between secretion of pulmonary mucus and calcium regulation was investigated. To confirm the effect of steroid hormones, immature mice were injected with estrogen (E2) or progesterone (P4) and mature mice were injected with dexamethasone (DEX). Subsequently, the location and expression of TRPV4, TRPV6, CaBP-9k, NCX1, and PMCA1 in lung tissue were examined. PAS staining was performed to investigate functional aspects of the protein expressions. There were no significant differences in calcium-related gene expressions in E2- and P4-treated mice, but TRPV4, NCX1, and PMCA1 were increased in DEX-treated mice and were recovered by RU486 treatment. This regulation is via the glucocorticoid receptor and is involved in the mucus secretion in the lung. TRPV4, TRPV6, CaBP-9k, NCX1, and PMCA1 were specifically expressed in Clara and alveolar type 2 cells of mouse lung. CC10, a marker of Clara cell, was decreased by DEX. In addition, mucin secretion, which is a functional aspect of this cell, was also decreased by DEX treatment. Control of calcium-related gene expression may affect the control of mucus secretion in the lung. Such a control mechanism can form the basis of studies into diseases such as inflammation due to mucus secretion abnormalities, coughing, and respiratory disorders and distress.

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P205

Effect of endocrine disrupting chemicals on the calcium channel and implantation during implantation period

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Miscarriage is a very common occurrence in humans, in which blastocyst implantation failure in naturally-occurring and assisted human reproduction occurs in up to 2/3 of all cases. Calcium (Ca^{2+}) has been showed to involve in many cellular signal transduction pathways as well as regulation of cell adhesion, which is necessary for the physiology process of endometrial epithelial cell transformation and stromal cell decidualization during embryo implantation. Previous studies have been reported that EDC can regulate the expression of genes associated with calcium transport in during pregnancy period such as TRPV6, PMCA, TRPV5, NCX1 and CaBP-D9k. Additionally, exposure to EDs during early gestation results in disrupt intrauterine implantation, uterine receptive, leading to implantation failure. In this study, BPA, OP, E2 and/or ICI 172,80 (antagonist) were inject by subcutaneous from 1 to 3 day post coitus. The number of implantation sites were significant decreased in OP group and no implantation site was observed in EDC + ICI groups. There was different in the expression of Ca channel between maternal uterine and implantation. The level of TRPV6, TRPV5 mRNA in uterus were significantly increased by EDC and/or ICI treatment. In contrary, their expressions are significantly decreased by OP- and BPA- treated in implantation site. The expression of NCX1 and PMCA1 mRNA level were significantly decreased in OP and BPA groups than that in the VE group. The expression of Muc-1 mRNA, a major epithelial apical surface glycoprotein expressed significantly decreased by OP-treated in implantation site. The mRNA level of E-cadherin, a group of cell surface glycoproteins responsible for maintaining adhesion between epithelial cells using a calcium-dependent mechanism was also significantly decreased in implantation site by BPA and OP treatment. Taken together, BPA and OP regulate the expression of calcium channel during early pregnancy period, throughout induce the loss numbers of implantation via reduce the uterine conceptive and implantation adhesion and invasion.

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P206

Clinical, paraclinical, etiological and therapeutic particularities of severe hypercalcemia: A comparative study

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Background
Severe hypercalcemia, defined as a serum calcium concentration $\geq$ 3.5 mmol/l or $>$ 3 mmol/l associated with symptoms and signs of acute calcium intoxication, is a rare but a potentially life threatening condition. The aim of this study was to assess clinical, paraclinical, etiological and therapeutic features of severe hypercalcemia and to determine its outcome.
Methods
It was a retrospective, descriptive and comparative study conducted in the department of internal medicine, Charles Nicolle hospital of Tunis, and including 32 patients with severe hypercalcemia (group 1) and 39 patients with non-severe hypercalcemia (group 2). Clinical, paraclinical, etiological and therapeutic characteristics were determined.
Results
Although demographic characteristics including age and gender were similar in both groups, an age $\leq$45 years was significantly associated with severe hypercalcemia (Hazard Ratio (HR) =4.69, P=0.02). This condition was identified with symptoms of hypercalcemia or a complication in 75% of cases (HR=5.35, P=0.001). Weakness (HR=5.04, P=0.01), anorexia (HR=2.7, P=0.04), nausea, vomiting and epigastric pain (HR=5.14, P=0.01), dehydration (HR=31.29, $P<0.001$) and renal failure (HR=4.26, P=0.01) were significantly associated with severe hypercalcemia. Its main etiologies were malignancy (43%), primary hyperparathyroidism (30%), medications (20%) and sarcoidosis (7%). The management of severe hypercalcemia involved both intensive medical and etiologic treatment. Saline rehydration, furosemide, calcitonin, bisphosphonate and hemodialysis were prescribed in 81%, 34%, 81%, 25%, 25%, 9% and 3% of cases, respectively. An immediate significant decrease of serum calcium level ($P<0.001$) was obtained in all patients with a normalization in 17% of cases. The mortality rate was 12% in group 1 and 13% in

group 2. The severity of hypercalcemia was not a predictive factor of mortality in our study.
Conclusion
Severe hypercalcemia is a therapeutic emergency including various symptoms. This condition can occur in multiple etiologies. Therefore plasma calcium should be measured at the slightest suspicion in order to perform an immediate and optimal management.

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P207

Genetic characteristics of sensitivity of vitamin D and prevalence of vitamin deficiency among patients of polyclinics

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Introduction
Vitamin D deficiency is a global problem worldwide.
Purpose of the study
To investigate the incidence of vitamin D deficiency and genetic sensitivity to it among patients in the polyclinic.
Materials and methods
A retrospective study was conducted, 6034 medical charts were analyzed, of those who were tested for vitamin D, the study included 567 patients (374 women, 193 men, women average age 40.7 ± 14.1 years, men – 41.3 ± 12.7 years). The following were analyzed: total calcium, creatinine, LDL, parathyroid hormone, urine protein. A genetic test was performed on the sensitivity of the receptors to vitamin D by sequencing HiSeq2000 on DNA chips (Illumina). An interpretation was made of the genetic characteristics of sensitivity to vitamin D: a predisposition to a decrease in receptor sensitivity; with a predisposition to high receptor sensitivity. The statistical analysis of the data was carried out with the help of the package of applied programs Statistica 10.0.1011.0. The critical level of reliability of the null hypothesis was assumed to be 0.05.
Results
Deficiency of vitamin D (25%, mean – 16.2 ± 3.4 ng/ml), moderate vitamin D deficiency (37%, mean – 24.9 ± 2.5 ng/ml), normal vitamin D concentration (38%, mean – 39.7 ± 9.6 ng/ml). A weak negative correlation was found between vitamin D and LDL ($P < 0.05$, $r = -0.16$). In the pairwise comparison (t-tests), significant differences in the seasons of the year were revealed for vitamin D levels: in winter groups (mean – 24.9 ± 9.97 ng/ml) and summer (mean – 31.2 ± 13.42 ng/ml), as well as in the autumn groups (mean – 29.8 ± 10.18 ng/ml) and spring (mean – 26.9 ± 10.9 ng/ml) ($P = 0.00003$ and $P = 0.01$ respectively). In the case of a pair comparison (t-tests), significant differences were detected by the level of total calcium and significantly differ in groups with stage 1 CKD (mean – 2.33 ± 0.1 mmol/l) from stage 2 CKD (mean – 2.38 ± 0.09 mmol/l) and from stage 3 CKD (mean – 2.53 ± 0.13 mmol/l) ($P = 0.017$ and $P = 0.0009$ respectively). In a pair comparison (t-test), significant differences in the level of vitamin D in groups with a predisposition to a decrease in receptor sensitivity (mean – 34.6 ± 10.54 ng/ml) and a predisposition to high sensitivity of receptors (mean – 28.3 ± 11.42 ng/ml) ($P = 0.015$).
Conclusions
The concentration of vitamin D by the genetic test is related to the sensitivity of the receptors.

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P208

A Curious phenomenon of Post radioiodine therapy induced hypocalcemia in Graves' disease: Case series

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Introduction
Graves' disease (GD) is often treated with radioiodine therapy for cure. While, post external irradiation and post-radioiodine therapy (RAI) induced hyperparathyroidism after many years of latency is a well known phenomenon, there are only anectodal reports of post-radioiodine hypocalcemia. The factors contributing to this are poorly understood. In this context, we evaluated our own series to look deeper in to this issue.
Material and methods
This retrospective study was conducted on 65 surgically managed GD patients. Diagnosis of GD was based on clinical picture, thyroid function tests, radionuclide scanning and histopathology. Exclusion criteria were subjects with vitamin D deficiency (20 ng/dl), chronic renal, hepatic or inflammatory disease or drugs interfering with calcium metabolism. All subjects were normocalcemic preoperatively (8.5–10 mg/dl). Hypocalcemia was treated with calcium supplements and vitamin D. Parameters such as severity of Graves' disease, Statistical analysis was performed by SPSS 20.0 version. Descriptive statistics, t test and Chi-square tests were performed.
Results
6/65 patients (9.3%) developed hypocalcemia. Average follow-up duration of subjects was 18.4 ± 4.5 months (14–24). Average onset of clinical and/or biochemical hypocalcemia was at 4.2 ± 1.5 months (2–7). Serum calcium level during first detection of hypocalcemia was 6.9 ± 1.5 mg/dl (5.6–8.2). Corresponding serum parathyroid hormone level was 35 ± 14 pg/ml (25–65). Hypocalcemia resolved after treatment for 2 months on an average. No further hypocalcemic episodes during follow-up period. Range of RAI dosage was 7–12 mCi. None of factors such as severity of hyperthyroidism, duration of hyperthyroidism, goiter size, age of patient, serum parathyroid hormone level and sex had statistically significant influence on occurrence of hypocalcemia on correlation and multivariate analysis.
Conclusions
Our study shows that post RAI hypocalcemia is a frequent morbidity. Further it is independent of any physiological or disease related factors. The exact cause of this curious phenomenon appears to be enigmatic, but we hypothesize that collateral damage caused by radiation causes temporary parathyroid stunning. More studies are needed to unravel this mystery, but active watch at followup post RAI therapy is recommended in routine management of GD.

Keywords: Graves' disease, Parathyroid hormone, hypocalcemia, Thyroidectomy, Radioiodine, Hypoparathyroidism

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P209

Primary hyperparathyroidism in the elderly

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Introduction
Primary hyperparathyroidism (PHPT) is the third most common endocrinopathy. Data on PHPT in the elderly are scarce.
Objective
To characterize elderly patients with PHTP, clinically and biochemically.
Patients
A total of 216 patients (73.6% females) aged ≥ 75 years were diagnosed and followed at a single tertiary medical center for PHPT.
Results
Mean follow-up was 11.3 ± 5.5 years. Age at diagnosis was 70.9 ± 7.2 years, and at last follow-up, 82.3 ± 5.2 years. Maximal serum calcium and maximal PTH were 11.6 ± 0.7 mg/dl and 3 ± 2.7 X upper limit of normal (UNL), respectively. Mean urinary calcium and vitamin D levels were 208 ± 130 mg/24 hours and 51.9 ± 19.1 nmol/l, respectively. Serum creatinine was 0.9 ± 0.5. Osteoporosis was diagnosed in 135 patients (62.5%; 92 with fractures, 75 after PHPT diagnosis), and nephrolithiasis, in 50; only 49 patients (22.7%) had neither. Thirty-six patients underwent parathyroidectomy: they were younger than the non-operated patients at diagnosis (67.4 ± 9.5 vs 71.6 ± 6.3 years) and had higher serum and urinary calcium levels. Patients ≥ 70 years at diagnosis ($n = 128$), compared to younger patients, had significantly lower levels of calcium (10.2 ± 0.7 vs 10.4 ± 0.8 mg/dl, $P = 0.05$) and PTH (1.7 vs 2.1 X UNL, $P = 0.05$) at last follow-up. The younger patients had more nephrolithiasis (29.9% vs 18.8%). In the whole cohort, serum and urinary calcium significantly ($P = 0.001$) decreased and vitamin D level significantly increased at last visit (10.3 ± 0.47, 172.5 ± 116, 68.6 ± 23, respectively) compared with levels at diagnosis (10.6 ± 0.7, 237 ± 148, 51.5 ± 19, respectively). Thirty-nine patients died during follow-up: they were significantly ($P = 0.001$) older than the remaining patients at diagnosis (75.2 ± 6.1 vs 70.2 ± 6.1 years) and last follow up (85.3 ± 5.9 vs 81.6 ± 4.8 years), with no differences in laboratory variables.

Conclusions
Most elderly patients with PHPT had at least one indication for parathyroidectomy, but only 17% were operated. Serum and urinary calcium levels decreased during follow-up.

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P210

Edentulous jaw and Primary HyperParathyroidism

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Introduction
Primary Hyperparathyroidism usually presents as bone disease, renal or with Gastro Intestinal Symptoms. Dental Symptoms as primary or presenting manifestations are rare. We report two patients who presented with edentulous jaw in young age, which resulted in investigations leading to the diagnosis for primary hyperparathyroidism.
Material and methods
We report two patients operated in a tertiary referral Centre from Jan 2017–Dec 2017 for PHPT with Edentulous jaw. We describe the clinical case and surgical findings of these two patients.
Results
First patient was a 30 year old lady had loosening and falling all teeth suddenly within 2 months, investigated had hypercalcemia of 13 mg/dl and had concordant Left Inferior parathyroid adenoma on USG and MIBI Scan. She underwent uneventful focused parathyroid with IOPTH monitoring and on follow up norm calcemic. Second patient was a 45 year old lady who had loosing and falling of most of the teeth with bone pains, investigated and found to have hypercalcemic crisis of 17 mg/dl. She had an aorta pulmonary window parathyroid Adenoma on functional and anatomic imaging. She was treated with hydration, Calcitonin and bisphosphonates and operated in the same admission and underwent sternotomy and focused parathyroidectomy with IOPTH monitoring and on follow up normocalcemic.
Discussion
Dental manifestations are rare but can be the first symptom of PHPT. Severe osteoporosis can manifest as falling of teeth when resorption of jaw occurs due to osteoporosis and tooth become loose and fall off.

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P211

Coeliac Disease complicating Autoimmune Hypoparathyroidism with Recalcitrant Hypocalcaemia

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We present the case of a 57 year old male that presented to a tertiary centre with a week's history of lethargy, muscle cramps and peri-oral paraesthesia. He was otherwise fit and well. His examination revealed no evidence of Chvostek's, Trousseau's or tetany. His reflexes were not assessed. Initial electrolyte screening confirmed a hypocalcaemia with a serum adjusted calcium of 1.47 mmol/l (2.2–2.6), his phosphate was elevated at 1.64 mmol/l (0.8–1.5) and a serum magnesium was below target range at 0.67 mmol/l (0.7–1.0). Serum PTH was 0.2 pmol/l (1.3–9.3). Vitamin D level was normal. Haematinics revealed a folate deficiency. USS of the neck identified no masses. Despite adequate parenteral replacement of Calcium, Magnesium, oral alpha calcidol and high doses of Vitamin D, his calcium levels remained low. As a work up for malabsorption, an IgA antibody screen returned positive and he was commenced on a gluten-free diet and treated for concurrent coeliac disease. Idiopathic hypoparathyroidism (IH) occurs with atrophic, infiltrative or autoimmune mediated destruction of the parathyroids. Injury must be severe as there is adequate reserve in a single parathyroid gland for normal function. It is distinct to the more common acquired hypoparathyroidism that occurs mostly after surgery and at a permanent incidence between 0.4 to 33% depending on the centre. The autoimmune hypoparathyroid patient load has been estimated via population studies at 3 per 100,000. The condition is recognised to be strongly associated with both adrenal antibodies (26%) and thyroid antibodies (12%), such that combinations of these contribute to the Autoimmune polyglandular syndrome type 1. APS1 has been associated with malabsorption in up to 15% of patients. However, despite epidemiological reviews recognizing the existence of coeliac disease as a co-morbid state sparse work has been done on the immunological factors underpinning it. Thus, Saha et al examined the co-presentation of this in 2016 and in a particular patient group of confirmed IH, found co-existing Coeliac Autoimmunity is present at 6.4% and biopsy proven coeliac disease at 1.2%. This is not significantly different from the incidence in the general population. These are small numbers when taken as per head of population, but they do present a confounding variable in the face of recalcitrant hypocalcaemia independent of copper or magnesium levels. The authors would therefore recommend anti-tissue transglutaminase antibody with total IgA levels to screen all similar patients as in our case, who can affirm compliance to medication.

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P212

The prevalence of Vitamin D deficiency in a Greek and a Cypriot population sample

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Introduction
The results of this epidemiological study demonstrate the burden of 25-hydroxyvitamin D deficiency in two sunny Mediterranean countries Greece and Cyprus- and some of the related risk factors. These two populations were examined together due to their common phylogenetic origin. Up until now there are no available data for the mean Vitamin D levels of the Cypriot adult population. An early identification of vitamin D deficiency is now considered as the cornerstone of preventive medicine.
Materials and methods
Vitamin D levels for 8780 Greek and 2594 Cypriot subjects were blindly collected from the hospitals' laboratory information systems over a 5-year time period. Sex, age, the month at which the blood sample was drawn, and accompanying diseases (recorded just for 870 patients in the Greek database) were also collected. These data were obtained respectively from the tertiary health care center AHEPA in Thessaloniki, Greece (latitude; N40.7°, longitude; E22.9°) and AGIOS LOUKAS a primary health care center in Nicosia, Cyprus (latitude; N35.1°, longitude; E33.3°). In order to examine the relationship between potential risk factors and vitamin D levels univariate analysis and multivariate linear regression analysis were performed.
Results
73.07% of the Greek and 69.28% of the Cypriot subjects of the sample had inadequate levels of vitamin D. The mean 25(OH)D value for the Greek subjects was found 25.08 ng/ml and for the Cypriots 25.37 ng/ml. The highest levels in both databases were recorded for the month September. For, both databases the multivariate linear regression models demonstrated that age and month were significantly associated with 25(OH)D levels. Sex was significantly associated only in the Greek database ($P<0.0001$). In the second multivariate linear regression model- which included just the subgroup of patients with a recorded disease- the month was not associated with 25(OH)D levels ($P=0.235$). Amongst the recorded diseases growth retardation, hypercalcemia, sickle cell anemia, polyneuropathy (all $P<0.01$), mental retardation and MS (both $P<0.05$) were related with 25(OH)D levels.
Conclusions
The prevalence of vitamin D deficiency is extremely high in both population samples and particularly in subjects with chronic diseases. However, the cross-sectional design of the study cannot prove causality and further prospective studies in healthy subjects are necessary.

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P213

Epidemiology of primary hyperparathyroidism in Santander, Spain

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Background and aims
Primary hyperparathyroidism (PHPT) is a common endocrine disorder with different epidemiological patterns among countries. The incidence of PHPT is unknown in Spain. The aim of our study is to assess the prevalence and incidence of diagnosed PHPT in adults between 1970 and 2014 in Santander, a population of 290.000 inhabitants, located in the north of Spain.
Subjects and methods
All patients diagnosed with primary hyperparathyroidism from 1970 to 2014 were included. PHPT was diagnosed when persistent hypercalcemia occurred with the presence of elevated or inappropriately normal parathyroid hormone levels. Prevalence and incidence density adjusted for age and sex were calculated for each 5-year period.
Results
We identified 709 patients (82.3% females) diagnosed with PHPT by the end of 2014. Females were older than males at baseline (median age 67.6 years (57.8–75.9) and 63.7 years (52.1–74.2) respectively) ($P<0.05$). Prevalence of PHPT was higher in females, and the female preponderance increased with age. In the mid-1990s the incidence rate in women was 3.72/100.000 person-years and doubled in the period 1995-1999, with an incidence rate of 8.38/100.000 person-years. Incidence increased in the following years, and in the period from 2005 to 2009, it doubled again from 12.08/100.000 person-years in 2000 to 2004 to a maximum level of 24.52/100.000 person-years in the period from 2005 to 2009. In the last period of study, from 2010 to 2014, the incidence in women decreased up to 21.44/100.000 person-years. The increased incidence is progressive and less flashy in males than females. The incidence in the period from 1995 to 1999 was 2.75/100.000 person-years and doubled in the period from 2010 to 2014, becoming 5.20/100.000 person-years. The prevalence of diagnosed PHPT in Santander increased from 0.01 per 1000 population in the period from 1980 to 1984 to 0.38 per 1000 population in the period from 2010 to 2014.
Conclusions
The incidence of PHPT in Santander continues its remarkable rise. The incidence of diagnosis is greater in females than in males and increases with age. The overall increase in incidence may be the result of more frequent plasma calcium measurements, periods of increasing medical interest or environment factors. However, the most likely explanation is the bias of the selective detection of PHPT in patients who are being evaluated for osteoporosis.

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P214

Human Chorionic Gonadotrophin (hCG) as a diagnostic test to differentiate between Parathyroid Carcinoma, Primary Benign Hyperparathyroidism and Secondary Hyperparathyroidism.

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Introduction
Parathyroid carcinoma (PCa) is a rare presentation of primary hyperparathyroidism (PHPT), accounting for less than 1% of cases. Differentiating parathyroid cancer from benign hyperparathyroidism is clinically challenging. Some previous work suggest that there is a paraneoplastic hCG production in parathyroid cancer (Stock et al 1987, Rubin et al 2008). In this study, we aimed to investigate whether the hCG+β kit from Roche Diagnostics could distinguish PCa patients from primary and secondary hyperparathyroidism. Additionally, we validate hCG levels according to renal function and determine hCG test sensibility and specificity to diagnose parathyroid cancer.
Material and methods
We studied a series of eight patients suffering from advanced PCa, referred to the CHU de Liege. A group of 20 PHPT patients and 25 patients with secondary hyperparathyroidism (SHP) due to chronic renal failure were used as controls. hCG+β kit on Cobas (Roche Diagnostics) uses 2 monoclonal antibodies that recognize holo-hCG, nicked hCG, β-core fragment and free β-subunit. Limits of hCG detection and quantification are <0.1 and <0.6 mUI/ml. In non pregnant and postmenopausal women and in men, hCG (p95) is <1 (5.3), <7 mUI/ml (8.3) and <2 (2.6) mUI/mL, respectively.
Results
The 8 PCa patients (3 women) presented high serum hCG values at: 1.29, 3.46, 5.7, 24.2, 31.2, 34.1, 36.5 and 164 UI/l. Values of 1.29 and 3.46 were obtained in 2 postmenopausal women. The lowest value was presented by the only still alive patient who had hormonal and biochemical normalization and tumor shrinkage induced by anti-parathyroid hormone immunotherapy (Betea et al. 2004). In cancer patients, there was a significant correlation ($r=0.786$; $P<0.05$) between hCG and PTH whereas median hCG (5.7 UI/l) was significantly higher than in PHP (1.25 UI/l) and SHP (0.97 UI/l). hCG test sensitivity was 75% and specificity was 94% to detect parathyroid cancer, with a cutt-off of hCG of more than 5.68 UI/l.
Conclusions
These results suggest that serum hCG might have the potential to discriminate between parathyroid adenomas and carcinomas, with a sensibility of 75% and a specificity of 94%. The only patient still alive who underwent a PTH immunotherapy, presented the lowest hCG values. If hCG could be predictive of PCa survival needs to be studied in a larger series of patients. A future area of research revealed by this data is to test hCG immunotherapy in parathyroid cancer.

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P215

Reliabilty of serum Calcium to Phosphorus (Ca/P) ratio as an accurate and inexpensive toolto define disorders of Ca-P metabolism: preliminary data

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Background
Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder. The Ca/P ratio is an accurate tool to differentiate patients with PHPT (>3.5 if Ca and P are expressed in mg/dl) from healthy subjects [1]. The reliability of this index is based on the fact that serum Ca and P are inversely related together. However, other disorders of the Ca-P metabolism, such as hypophosphoremia (HypoP), might impair the Ca/P ratio.
Aim
To validate the accuracy of Ca/P ratio in the diagnosis of Ca-P metabolism disorders, including also patients with documented HypoP.
Methods
A single-center, retrospective, case-control study was carried out, including 130 patients with documented PHPT and 300 patients with HypoP, compared with 120 controls. HypoP patients were enrolled among HIV-infected patients on HAART treatment from the large Modena cohort. The main outcome measures were: serum Ca, P, parathyroid hormone (PTH), 25-OH vitamin D, albumin and creatinine.
Statistical analysis
Comparisons among groups were performed by the nonparametric Kruskal-Wallis, followed by the Dunn's post hoc test. The diagnostic accuracy of Ca/P ratio was investigated by receiver operator characteristics (ROC) curves in order to define cut-off points (with the highest sensitivity and specificity).
Results
The Ca/P ratio was significantly higher in the group of PHPT together with HypoP, compared to controls ($P<0.0001$). Also Ca and PTH were significantly different among groups, in particular they were higher ($P<0.0001$) in PHPT than both controls and HypoP, as expected. At ROC curves analysis, the cut-off of 3.6 for Ca/P ratio was able to identify patients with PHPT and HypoP (sensitivity 91%; specificity 93%). Among patients with Ca/P ratio above 3.6, the thresholds of 10.2 mg/dl for serum Ca (sensitivity 91%; specificity 98%) and of 83.6 pg/ml for PTH (sensitivity 92%; specificity 93%) were defined for the specific diagnosis of PHPT.
Conclusions
In this study we confirm the role of serum Ca/P ratio as a reliable index to diagnose a Ca-P metabolism disorder, especially PHPT and HypoP. In clinical practice, when a Ca/P ratio above 3.6 is found, the presence of serum Ca >10.2 mg/dl or PTH >83.6 pg/ml is able to discriminate patients with PHPT from those with HypoP.

Reference
1. Madeo *et al*, Serum Calcium to Phosphorous (Ca/P) Ratio Is a Simple, Inexpensive and Accurate Tool in the Diagnosis of Primary Hyperparathyroidism. JRBM Plus, 2017. DOI: 10.1002/jbm4.10019.

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P216

Secondary hyperparathyroidism after obesity surgery is associated with serum levels of 25-hydroxyvitamin D and ionized calcium

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Background
Secondary hyperparathyroidism (SHPT) is common in obesity, and a concern after obesity surgery due to negative impact on bone. Longitudinal data is sparse, and relationships with vitamin D and calcium levels are unclear. We studied the prevalence of SHPT over five years after Roux-en-Y gastric bypass (RYGB) and investigated whether SHPT was associated with serum levels of 25-hydroxyvitamin D (25(OH)D) and ionized calcium (iCa).
Methods
347 of 568 (61%) patients attending a 5-year follow-up visit after a RYGB at Oslo University Hospital in the years 2004-2008 were eligible for study inclusion. We excluded 14 patients with missing data, four with primary hyperparathyroidism and 10 with elevated serum creatinine. We defined SHPT as PTH >7.0 pmol/l and vitamin D deficiency as 25(OH)D <50 nmol/l. Low iCa refers to serum levels <1.21 mmol/l (lower tertile of reference range or below). Substitution of vitamin D3 (1000 IE/day) and calcium carbonate (1000 mg/day) was recommended.
Results
Among the 319 included patients (230 women) the prevalence of SHPT was 32% before surgery, while the prevalence was 18%, 24%, 28% and 35% after a half, one, two and five years, respectively. Vitamin D deficiency was found in 45% preoperatively, and 18%, 20%, 28% and 33% after a half, one, two and five years. The proportion with serum iCa in the lower range was: 24% preoperatively, and 29%, 35%, 44% and 49% at a half, one, two and five years. Table 1 illustrates the prevalence of SHPT by serum vitamin D and calcium levels (*illustrates $P<0.001$ between subgroups).

Table 1

	Baseline	1/2y	1y	2y	5y
25(OH)D (nmol/l)					
<50	40	34	29	45	39
≥ 50	26*	13*	20*	19*	33^{ns}
Ionized calcium (mmol/l)					
<1.21	46	21	30	35	46
≥ 1.21	26*	16*	22*	22*	23*

Discussion
The prevalence of SHPT decreased the first half year after RYGB and thereafter increased over time. SHPT was higher in vitamin D deficiency and with iCa levels in the lower range. Improved vitamin D and calcium status may potentially reduce the prevalence of SHPT both preoperatively and after obesity surgery.

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P217

The frequencies of persistent hyperparathyroidism and hypercalcemia after kidney transplantation: a single-center experience

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Bone mineral disorders usually resolve after successful kidney transplantation. Serum calcium (Ca), phosphorus (P) and parathyroid hormone (PTH) levels tend to normalize within time. Serum Ca levels >10.2 mg/dL and PTH levels >150 pg/mL at 6th−12th months of transplantation is defined as persistent hypercalcemia and persistent hyperparathyroidism (PHPT) in recipients with normal graft function. Reported persistent hypercalcemia prevalence varies in wide range between 5% and 66%. This huge variation might be explained with different diagnostic criteria, heterogenic recipient population and variation in renal replacement vintage. We aimed to evaluate the prevalence of hypercalcemia and PHPT among recipients after successful kidney transplantation in our center.
Methods
We performed a retrospective study involving a total 391 (224 males, 40.6 ± 11.9 years) adult kidney transplant recipients between January 2008 and December 2014. Recipients who were underwent parathyroidectomy before transplantation were excluded. Demographic and laboratory data of 307 recipients who were followed up at least 12 months were obtained by review of electronic file system. PHPT was defined as serum corrected Ca level >10.2 mg/dl (at least twice in a 6 month period) and PTH >150 pg/ml at 6th month of transplantation. Serum creatinine, Ca levels at pre- and post-transplant 1st, 3rd, 6th, 12th months, PTH levels at pre- and post-transplant 6th, 12th months of recipients were recorded.
Results
A total 307 recipients (150 deceased, 157 living donor; 175 male, 132 female; mean age 39.4 ± 11.4 years) were enrolled the study. The mean duration of renal replacement treatment was 75.1 ± 3.3 months. Mean serum Ca levels before transplantation and at 1st, 3rd, 6th, 12th months of transplantation were 9.3 ± 0.8 mg/dl, 9.3 ± 0.7 mg/dl, 9.6 ± 0.7 mg/dl, 9.7 ± 0.7 mg/dl, 9.7 ± 0.7 mg/dl; and prevalence of hypercalcemia (>10.2 mg/dl) at 1st, 3rd, 6th, 12th months of transplantation were 10.8%, 21.2%, 21.2% and 21.2%, respectively. Mean serum PTH levels before transplantation and at 6th, 12th months of transplantation (>150 pg/ml) were 526.2 ± 474.9 pg/ml, 237 ± 334 pg/ml, 215 ± 236.9 pg/ml, and prevalence of hyperparathyroidism at 6th, 12th months of transplantation were 57.1% and 52.3%, respectively.
Conclusion
PTH levels decreased and Ca levels remained stable after transplantation within 12 months in our study. Although prevalence of hyperparathyroidism was high, persistent hypercalcemia affected fewer recipients.

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P218

Prevalence and clinico-epidemiology of vitamin D deficiency in patients with type 2 diabetes mellitus and hypertension – a Pan-India study

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Introduction
Vitamin D (vitD) deficiency is a worldwide epidemic health problem, with a prevalence of about 70–100% in general Indian population. The objective of this cross-sectional, clinico-epidemiological, Pan-India study was to evaluate the prevalence of vitD deficiency in patients with Type-2 diabetes mellitus (T2DM) or hypertension (HT) or both T2DM and HT and to understand the management practices in Indian real-world setting.
Methods
Adults with a diagnosis of T2DM or HT or both (established/newly diagnosed), visiting physician for routine check-up, were enrolled. Percentage of patients with vitD deficiency in those with T2DM/HT/or T2DM + HT and prevailing management practices were assessed. VitD insufficiency and deficiency was defined as serum 25(OH)D levels 21–29 ng/ml and ≤ 20 ng/ml, respectively.
Results
A total of 1501 (99.5%) patients completed the study (T2DM:500 [99.2%]; hypertension:499 [99.6%]; both T2DM and HT: 502 [99.8%]). Mean ($\pm$s.d.) age of the study population was 52.9 ± 12.49 years. Mean age at diagnosis of vitD deficiency was 52.5 ± 10.77 years; mean vitD level at the time of diagnosis was 16.9 ± 12.78 ng/ml. Overall prevalence of patients with low vitD levels (vitD deficiency and insufficiency) was 1257 (83.7%); 1231 (82%) were newly diagnosed cases. Out of 1257 (83.7%) patients with low vitD levels, 60.9% patients had vitD deficiency and 22.9% patients had vitD insufficiency. Prevalence of low vitD levels amongst patients with T2DM ($n=500$), HT ($n=499$) and T2DM + HT ($n=502$) was 84.2%, 82.6% and 84.5%, respectively. Out of 1257 patients with low level of vitD, 84.8% received vitD supplementation. Preferred dose of vitD was 60,000IU (70.2%); route of administration was oral for majority of patients (79.6%). Preferred frequency of

dose was once in a week (76.7%). Average duration of treatment was 7.6 ± 3.49 weeks. Factors considered by physician to prescribe vitD supplements were vitD deficiency (26.9%), vitD insufficiency (34.5%), symptoms of vitD deficiency (10.4%) and co-morbid condition (1.8%). Out of 126 patients with low vitD levels and T2DM, 84.37% patients had abnormal HbA1c levels.
Conclusion
Prevalence of vitD deficiency was higher amongst newly diagnosed cases, which indicates that vitD deficiency may have been missed in a large proportion of patients with T2DM, HT, or both T2DM and HT. This study emphasizes on the magnitude of overlap between these diseases and the need for routine vitD screening and appropriate management in Indian patients with T2DM and HT.

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P219

PTH threshold for hyperparathyroidism diagnosis in vitamin D deficiency

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Introduction
Vitamin D insufficiency is very common among Spanish adults. It is well established there is an inverse relationship between vitamin D and PTH levels. The diagnostic approach of an increased serum PTH concentration in a normocalcemic normophosphatemic patient is frequent in routine practice and the deficiency of vitamin D is the major cause of secondary hyperparathyroidism (SHPT). The aims of this study were to evaluate the prevalence of SHPT in a cohort of normocalcemic patients with elevated serum PTH levels and deficiency/insufficiency of vitamin D and to analyze the correlation between PTH and vitamin D levels.
Methods
96 patients with elevated PTH levels and a 25OHD <30 ng/ml were included. All patients were treated with vitamin D for 3–6 months and all parameters were re-evaluated. Patients with diabetes and chronic kidney disease were excluded.
Results
96 patients were included (61.3% female; 63.22 ± 12.56 median age). Baseline characteristics were: Serum calcium: 9.87 ± 0.93 mg/dl, serum phosphate: 3.08 ± 0.54 mg/dl, calciuria: 180.3 ± 123 mg/dl/24 h, PTH: 117 ± 42 and 25(OH) vitamin D: 14.86 ± 3.3 ng/dl. After treatment with vitamin D there was a significant increase of 25(OH) vitamin D levels (40.36 ± 19, $P<0.0001$) and a significant decrease of PTH levels (83 ± 40 $P<0.001$), serum calcium (9.8 ± 0.58, $P<0.037$), and calciuria (199 ± 123 mg/24 h; $P<0.032$). 12 patients were diagnosed of primary hyperparathyroidism (12.5%). Plasma 25(OH)D3 levels correlated negatively with PTH levels ($r=-0.261$, $P<0.01$). For the diagnosis of hyperparathyroidism in patients with vitamin D levels low 20 ng/ml the threshold of 108.5 pg/ml for PTH levels was obtained by means of the ROC curve analysis, with 87% of sensitivity and 58% specificity.
Conclusions
Vitamin D deficiency/insufficiency is the major cause of secondary hyperparathyroidism. To adequately assess this condition is critical to replenish levels of vitamin D. PTH threshold for hyperparathyrodism diagnosis in vitamin D deficiency must be calculated.

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P220

Vitamin D status in hospitalized chronic ill patients

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Objectives
Vitamin D deficiency is rarely considered or treated in critically ill patients. Deficiency of 25-hydroxy vitamin D (25(OH) D) prior to hospital admission might be a significant predictor of short and long term all cause patient mortality in a critically ill patient. We aimed to investigate the prevalence of vitamin D deficiency in hospitalized patients and its relation to the length of stay and outcome of hospitalization.
Methods
Prospective cohort study performed on eighty patients admitted to internal medicine department, with acute deterioration of their chronic illness. Four groups of diseases were included, namely chronic liver diseases, chronic obstructive pulmonary diseases, cerebrovascular stroke and heart failure. The patients were followed up till their discharge, or transfer, or death. Patients were sampled for their vitamin D level on admission and were divided according to their vitamin D status into sufficient, insufficient and deficient. Statistical methods and analysis of the present study was conducted using SPSS V17 program.
Results
Vitamin D level had a significant inverse correlation with length of hospital stay ($r=-0.648$) ($P=<0.001$). In vitamin D deficient and insufficient groups, there was a significant difference between survivors and non-survivors as regard vitamin D levels and inverse correlation between vitamin D level and outcome of hospital admission.
Conclusions
Vitamin D deficiency and insufficiency are significantly associated with a longer hospital stay and a poor outcome of hospital admission in comparison to control.

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P221

Role of 4D–TC in Primary Hyperparathyroidism Diagnosis– case report

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Introduction
Primary Hyperparathyroidism (pHPT) is a calcium metabolism disease, resulting from one or more parathyroid glands hyperfunction. Ultrasonography and Technetium Sestamibi are, nowadays, the first line imaging techniques for diagnosis. Recently, a 4-dimensional computed tomography (4D-TC) protocol has emerged, presented in the last endocrine surgery guidelines. It is a dynamic imaging exam based on the parathyroid contrast uptake pattern, whose sensitivity and specificity have been shown to be superior to conventional imaging tests. 4D-TC allows a better anatomic, morphologic and functional precision for detection of parathyroid lesions either of typical or ectopic location.
Clinical case
76 years-old man, with history of arterial hypertension, renal microlithiasis and prostate neoplasm, evaluated in endocrinology department for nodular thyroid disease and osteoporosis. In routine laboratory test, it was detected hypercalcemia (11.3 mg/dl), normal phosphatemia (2.6 mg/dl), elevated parathormona (PTHi 169.2 pg/ml), normal creatinine (1.1 mg/dl) and normal 24 h urinary calcium level. Either, ultrasonography and Sestamibi were negative for parathyroid lesions. Because of the presence of three surgery criteria (hypercalcemia, osteoporosis and renal lithiasis), it was decided to perform a preoperative 4D-TC, which revealed a parathyroid adenoma in the lower third of right thyroid lobe with 9 × 20 mm. A parathyroidectomy was performed without complications and intraoperative PTHi levels vary from basal value of 164.9 pg/ml to 55 pg/ml after procedure. The histologic report confirmed parathyroid adenoma. Last analytical evaluation showed maintained normal serum values of calcium (9.4 mg/dl) and PTHi (70 pg/ml).
Discussion
This clinical case portrays a pHPT diagnosis in which only the 4D-TC, allowed the identification and location of the underlying lesion, after conventional first-line imaging tests were negative. It was our purpose, to demonstrate the potential of 4D-TC as an effective method to identify parathyroid lesions, especially in cases of difficult detection, constituting a useful tool in the preoperative evaluation. Its use, replacing conventional exams, may happen if more studies confirm its diagnostic superiority.

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P222

Severe hypomagnesaemia and hypocalcaemia: an uncommon but serious complication with proton pump inhibitor therapy

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A 73 year old man was admitted to the hospital with a multi-factorial fall. He was otherwise asymptomatic. Past medical history included stage 3 chronic kidney disease (CKD), ulcerative colitis, epidermolysis bullosa and mild cognitive impairment. Examination was unremarkable apart from unilateral leg swelling and deep venous thrombosis was excluded. Investigations showed incidental undetectable magnesium level and severe hypocalcaemia. Potassium level was normal, 25-hydroxy-vitamin D level was low and parathyroid level was appropriately raised. Electrocardiogram revealed normal sinus rhythm and high corrected QT interval. Treatment with intravenous magnesium and calcium rendered both electrolytes to normal. Medication review revealed omeprazole 20 mg once a day for more than 2 years for heartburn. He was not on diuretics and there was no suggestion of alcohol excess, diarrhoea or re-feeding syndrome. Hypomagnesaemia was attributed to the long term use of the omeprazole and the latter was replaced with ranitidine. He did not require further magnesium or calcium replacement and was commenced on cholecalciferol replacement for vitamin D deficiency. Proton pump inhibitor (PPI) induced hypomagnesaemia is rare but potentially serious complication of long term PPI use. Hypomagnesaemia is caused by reduced intestinal absorption of magnesium and seems to be a class effect seen with all PPIs. The severity of hypomagnesaemia is not linked to the dose of PPI but to the duration of use. The risk is higher in elderly population, females, people with concomitant diuretic use and with other co-morbidities especially diabetes or diarrhoea. Hypomagnesaemia can be associated with hypocalcaemia and hypokalaemia. Patients present with weakness, diarrhoea, leg cramps, paraesthesia, tetany, seizures and torsades de pointes. Physicians must recognise this potentially serious complication and switch patients from PPIs to H2-receptor blockers as the latter are not associated with abnormal magnesium absorption. Short term management involves replacement of magnesium, calcium and potassium. Cardiac monitoring in indicated especially in patients with prolonged QT interval. Risk benefit analysis should be carried out for patients in whom long term PPI therapy is being considered.

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P223

Hip fractures and vitamin D deficiency

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Introduction
Vitamin D deficiency is associated with the development of osteomalacia, as it decreases intestinal calcium absorption and bone mineralization. However, severe vitamin D deficiency may also be correlated with secondary hyperparathyroidism which induces osteoporosis. In addition, it induces muscular dysfunction which along with frailty in old age it may induce falls.
Aim
The aim was to present a group of patients with severe vitamin D deficiency who developed a hip fracture.
Methods
A group of ten old frail patients, aged 82–97 years, is presented, who developed a hip fracture. Patients were successfully operated for the hip fracture. Laboratory evaluation revealed marginally low blood calcium, low urinary calcium and very low $25(OH)D_3$ levels ($25(OH)D_3$ <7 ng/ml, normal range >30 ng/ml).
Results
Cholecalciferol was administered to the patients initially in high dosage, thereafter in lower doses. The patients recovered fully. A period of six months after discharge from the hospital they were reevaluated. They had normal $25(OH)D_3$ levels and they had recovered, physical condition found to be similar to that previous to the hip fracture.
Conclusions
In the group of patients with hip fracture presented the observed severe vitamin D deficiency contributed to the development of hip fracture, whereas the administered vitamin D acted therapeutically and contributed to the postsurgical rehabilitation of the patients. Thus, it is recommended that in old patients presenting with a hip fracture vitamin D levels should be measured and the respective vitamin D deficiency should be corrected therapeutically with the administration of cholecalciferol. In frail patients who live in closed accommodation, due to inability to get out, the measurement of vitamin D should be performed. Vitamin D administration is recommended for the prevention of falls and fractures in this group of patients.

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P224

Clinical manifestation of Hypoparathyroidism in a monocentric cohort: our experience

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Introduction
Hypoparathyroidism (HP) is characterized by low serum calcium and increased phosphate levels associated with inappropriately low serum PTH levels. Clinical manifestations of HP are tingling, muscle cramps, seizures, nephrocalcinosis, kidney stone, kidney failure, depression and anxiety.
Objective
Quantify the chronic symptoms and complications of HP in our monocentric cohort.
Material and methods
We conducted a retrospective study involving patients that attended the Endocrinology Unit of S.Orsola-Malpighi Hospital in Bologna from 1980 to 2016. HP was confirmed by hypocalcemia with a simultaneous low or inappropriately normal PTH level for at least 1 yr. We evaluated serum and urine laboratory results in association with clinical manifestation.
Results
We identified 130 permanently hypoparathyroid patients. Mean age at the end of the observation period was 61 ± 16 (range 21–94) yr, and the cohort was 83% female. The main cause of HP was neck surgery. 90.8% of patients were treated with calcium supplements (mostly carbonate) and/or calcitriol. In addition, 14.6% took thiazide diuretics and 7.7% phosphate binders. Mean serum calcium was 8.4 ± 0.8 mg/dl. Time-weighted average for calcium was between 7.5 and 9.5 mg/dl for 80.8% of patients, while 12.3% was under this target and 6.9% over the target. The average calcium-phosphate product was 38.3 ± 6.9 mg^2/dl^2, and 98.4% had a calcium-phosphate product under 55 mg^2/dl^2. Hypercalciuria was recorded in 27.7% of the cohort. Calcium urinary levels were correlated with age ($P=0.009$), serum calcium levels ($P=0.001$) and calcitriol dose ($P=0.005$). As expected, neuromuscular symptoms were inversely correlated with serum calcium levels, and only 8% of patients with calcium levels under 9 mg/dl was symptomatic. Nevertheless, 50% of patients were asymptomatic with calcium levels under 6.5 mg/dl. Symptomatic hypocalcemia and vitamin D intoxication required hospitalization in 6 and 11 occasions, respectively. Chronic kidney disease (CKD) was observed in 27.7% of the cohort. Thirty patients developed moderate CKD and six severe CKD. By multivariate Cox regression, eGFR was inversely associated with serum calcium levels ($P=0.04$; HR 1.7 CI 95% 1.0–2.9). Nephrolitiasis was detected in 14.6% and nephrocalcinosis in 2.3% of the cohort. Soft tissue calcifications were observed in 14.6% of the cohort. Bone fractures occurrred in 15.3% (20/130) of patients, while 19.3% (12/62) had a densitometric diagnosis of osteoporosis. In addition, hospitalization for cardiovascular events (20.8%), malignancy (10%), and infections (7.7%) were recorded.
Conclusions
Hyoparathyroidism and its treatment are associated with a high rate of complications, particularly kidney disease.

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P225

Primary hyperparathyroidism due to a parathyroid adenoma with cystic degeneration presenting as recurrent acute pancreatitis

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Primary hyperparathyroidism (PHPT) is rarely associated with the development of acute pancreatitis (AP). The incidence of AP induced by hypercalcemia in PHPT varies between 1.5 and 7%. PHPT is most commonly caused by parathyroid adenoma and infrequently by parathyroid hyperplasia, carcinoma or cyst and multiple endocrine neoplasia (MEN) types 1 and 2A. The present case is a 48-year-old man referred to our service for further investigation 1 month after an acute hemorrhagic necrotic pancreatitis in context of hypercalcemia, complicated with caudal pancreatic pseudocyst, partial thrombosis of portal vein, hepatosplenomegaly, moderate anemia and acute renal failure. His history included 3 AP attacks managed conservatively throughout the last 2 years, left renal microlithiasis, essential hypertension, chronic renal insufficiency, hyperuricemia, without additional risk factors for AP like alcohol ingestion, hyperlipidemia and gallstones. Laboratory findings revealed increased serum ionized calcium (6.29 mg/dl) and total serum calcium (11.98 mg/dl), hypophosphatemia (2.06 mg/dl) associated with elevated parathyroid hormone (PTH = 320 pg/ml), high serum amylase (167 U/l), lipase (318.8 U/l), C-reactive protein (9.94 mg/dl), azotate retention (creatinine = 1.75 mg/dl, serum urea = 47 mg/dl), hyperglycemia (130 mg/dl) and moderate anemia (haemoglobin = 9.3 g/dl). Cervical ultrasonography showed a 5.8/4.04/3.74 cm, mixed, echogenic and transonic, well-defined mass located postero-inferior of the right thyroid lobe. Single photon emission computed tomography (SPECT) with technetium-99 m sestamibi combined with X ray–based computed tomography (CT) revealed a right posterior cystic parathyroid adenoma, extended in the superior mediastinum, measuring 5/3.5/4 cm. After conservative management, hydratation, forced diuresis and calcitonine, the patient underwent right inferior parathyroidectomy. Histopathological examination confirmed the diagnosis of parathyroid adenoma. Postoperatively, the patient developed mild hypocalcemia and was treated by intravenous calcium infusions, followed by oral calcium and vitamin D. Serum calcium and PTH levels returned to normal and the patient was asymptomatic at the follow-up examinations. Although hypocalcemia is expected to appear during an AP attack, identifying hypercalcemia should always raise the suspicion of either hyperparathyroidism or malignancy. High PTH helps differentiate the two. As AP can have fatal consequences, it is important to reassess calcium levels after resolution of AP, especially in patients with idiopathic recurrent AP, because early recognition and treatment prevent reappearance.

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Glucose metabolism in primary hyperparathyroidism: The role of parathyroidectomy

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Background
Although primary hyperparathyroidism (PHPT) has been associated with diabetes mellitus (DM), the etiological link is not clear and the effect of parathyroidectomy is controversial.The aim of this observational study was to investigate the metabolic link between calciotropic hormones and glucose metabolism in PHPT patients before and after parathyroidectomy.
Methods
Twenty-four consecutive patients with PHPT (Group-A) without DM were included in the study. Anthropometric characteristics and medical history were recorded. Fasting plasma glucose (FPG), fasting insulin (FI), calcium, phosphorus, parathyroid hormone (PTH) and 25-hydroxyvitamin-D [25(OH)D] were measured. Homeostasis Model Assessment was used for estimating insulin resistance (HOMA-IR) and β-cell function (HOMA-B). QUICKI index for insulin sensitivity was also calculated. In a subgroup of 13 patients (Group-B) a scheduled curative parathyroidectomy was performed and all measurements were repeated after surgery. In 10 out of 13 a 75 g OGTT was performed before and 6 weeks after surgery to further evaluate glucose response, insulin response and insulin sensitivity using Matsuda Index. SPSS 22 was used for statistical analysis.
Results
Group-A had a mean age of 55 ± 10.66 years and the female:male ratio was 19:5. Pearson and Spearman correlation coefficient was used and a statistically significant positive correlation between HOMA-B and PTH ($r = 0.53$, $P = 0.008$) was identified. PTH was also correlated to waist-to-hip ratio ($r = 0.44$, $P = 0.03$) and inversely to FPG/FI ratio ($r = -0.40$, $P = 0.056$). Linear regression showed a significant linear relation between HOMA-B and PTH ($P = 0.006$), which remained significant when adjusted for age and BMI.When subjects were classified according to their 25(OH)D levels in vitamin D sufficient [25(OH)D ≥ 20 ng/dl, $n = 16$] and vitamin D insufficient ($10 < 25(OH)D < 20$ ng/dl, $n = 8$), independent samples *t*-test showed no significant difference in glucose homeostasis. In Group-B after surgery, calcium and PTH levels normalized and phosphorus increased. T-paired test and Wilcoxon signed rank test were used but no significant alterations were identified in FPG ($P = 0.56$), FI ($P = 0.73$), HOMA-IR ($P = 0.65$), HOMA-B ($P = 0.53$), QUICKI ($P = 0.90$), Matsuda index ($P = 0.10$), BMI ($P = 0.17$).The correlation between HOMA-B and PTH remained significant after surgery ($r = 0.76$, $P = 0.002$).
Conclusion
Findings of this small study indicate a correlation independent of vitamin D between PTH and indices of β-cell function and insulin sensitivity, in PHPT patients. This parallel increase of HOMA-B and PTH could be due to insulin resistance or reflect a potential direct action of PTH on β-cell. Larger studies will clarify the mechanisms and explain the inability of parathyroidectomy to reverse this effect.

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Acquired Fanconi syndrome and hypophosphatemic osteomalacia in two patients treated with adefovir and tenofovir

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Background
Proximal tubule dysfunction in Fanconi syndrome causes impaired reabsorbtion of amino acids, glucose, urate and phosphate, which leads to hypophosphatemic osteomalcia. Adefovir and tenofovir are two nucleoside reverse transcriptase inhibitors, which are used for treatment of patients with hepatitis B infection. Although these drugs are well tolerated with few side effects, patients may rarely suffer from drug-induced Fanconi syndrome and hypophosphatemic osteomalacia.
Clinical case
Patient-1, a-63-year-old male patient, referred to Endocrinology and Metabolism Clinic suffering from right knee pain for 3 months which became bilateral in course of time. He also had pain in lomber region, in legs and feet. He has been on adefovir treatment for hepatitis B infection for 10 years. His phosphorus (P) level was 1.1 mg/dl, calcium (Ca) level was 9.05 mg/dl and ALP level was 153 mg/dl. His tubular maximum of phosphate corrected for GFR was low for his GFR, age and gender. His FGF23 level was suppressed. After treatment with calcitriol 50 μg and with 1500 mg/day phosphorus, his phosphate levels reached to normal levels with amelioration of symptoms within 1 year and dose was tapered according to clinical and laboratory assessment. Patient-2-, a 64-year-old-male patient, applied to Endocrinology and Metabolism Clinic suffering from loss of balance, difficulty in walking, bilateral hip and knee pain and general muscle pain for 4 years. He had been walking with the help of crutch for 2 years. He was on treatment with tenofovir for 5 years for hepatitis B infection. His serum Ca was 8.78 mg/dl, P was 1.2 mg/dl and ALP level was 242 mg/dl. His tubular maximum of phosphate corrected for GFR was low for his GFR, age and gender. He is on treatment with calcitriol 0.25 μg and 1500 mg/day phosphorus with normalization of calcium and phosphorus levels as well as amelioration of symptoms. Due to previous lamivudine resistance, entacavir treatment was recommended after cessation of tenofovir for treatment of hepatitis B infection.

Conclusion
Drug induced Fanconi syndrome and hypophosphatemic osteomalacia should be kept in mind in patients receiving nucleoside analogue treatment for hepatitis B who suffer from bone pain and muscle weakness.

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P228

The coexistence of primary hyperparathyroidism with different auto-antibodies and autoimmune diseases

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Introduction
The coexistence of primary hyperparathyroidism with autoimmune diseases is described very rarely in the literature so far. There are only few cases of immune-mediated hyperparathyroidism, associated with anti-calcium- sensing receptor autoantibodies, frequently in context with other immune diseases. Spontaneous remission of primary hyperparathyroidism in anti-TNF therapy of psoriatic arthritis has also been described in one case. Prevalence of positive antithyroid antibodies is 10–13%, and prevalence of undiluted antinuclear antibodies is up to 20% in general population.
The aim of the study was to examine the prevalence of positive autoantibodies in patients with primary hyperparathyroidism.
Material and methods
The study was conducted on 38 patients with primary hyperparathyroidism. Data were collected from medical records. Laboratory or medical history evidence of autoimmune diseases were collected.
Results
Autoimmune thyroid disease was present in 13 (36.1%) of 36 patients. Antinuclear antibodies and antinuclear antibodies on HEP-2 were positive in 4 (22.2%) of 18 patients. Tissue transglutaminase antibodies were done in 14 patients, and were negative in all cases. Antineutrophil cytoplasmic antibodies were done in 13 patients and were negative in all cases. Anticardiolipin antibodies were negative in all 14 cases. Of all 38 patients, 16 (44,4%) of them have either an autoimmune thyroid diseases or some other proven autoimmune disease.
Conclusion
In patients with primary hyperparathyroidism, there is a higher prevalence of autoimmune thyroid disease and positive antinuclear antibodies to HEP-2 than in the general population. Also, the presence of some autoimmune disease in 44.4% of patients is surprisingly high. We propose to examine the prevalence of anti-calcium-sensing receptor autoantibodies in patients with the simultaneous presence of primary hyperparathyroidism and other autoimmune diseases.

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P229

Timely and dose assessment of serum parathormone and calcium levels by cinacalcet in patients with primary hyperparathyroidism: an individualized approach

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Objective
To assess the regulation of parathormone (PTH) and serum calcium (s-Ca) in patients, on follow-up over a long time period of four years, who have primary hyperparathyroidism (pHPT) and whose condition is non-operable or who are not willing to undergo surgery.
Methods
Initially, 17 patients with documented pHPT were recruited and treated with calcimimetic cinacalcet at a dose calculated according to s-Ca levels ($\leq$11 mg/dl or $>$11 mg/dl), amounting to 30–60 mg/daily ($n=8$) and 60–90 mg/daily ($n=9$). All the patients but four underwent PTH and s-Ca monitoring, firstly after 3 months and then every 6 months, together with monitoring of s-phosphorus, 25-hydroxy-vitamin D [25(OH)D] levels, and a yearly bone mineral density (BMD) check. No patients were taking other drugs, except for cholecalciferol compounds. To compensate for the small number of patients, we analyzed both mean and median values and parametric and non-parametric analysis was performed.
Results
Gr1 ($n=7$) and Gr2 ($n=6$) were matched by age 66 ± 9.2 yr vs. 69.5 ± 6.5 yr. S-Ca levels were statistically significantly (ss) higher at baseline in Gr1 (11.3 ± 0.2 mg/dl) than in Gr2 (10.7 ± 0.2 mg/dl; $P<0.002$). PTH levels were higher, though not ss, in Gr1 (262.8 ± 114.9 pg/ml) than in Gr2 (180.5 ± 17.1 pg/ml). A steep and rapid reduction of PTH was observed in Gr1 at month 3 (M3) resulting in a lower mean and median vs Gr2 for this time point as well as for the following assessments. After M24 and until M48, mean and median values for PTH were close for the 2 groups (M24: 126.6 ± 31.2 pg/ml vs. 118 ± 33.3 pg/ml; M48:95.3 ± 22 pg/ml vs.100.3 ± 9 pg/ml). A consistently increasing level of 25 (OH) D was noted throughout the study in both groups, peaking at M36. No difference in the z-score between both groups was registered. BMI tendentially decreased in both groups.
Epicrisis
Cinacalcet was effective in controlling s-Ca and reducing PTH levels in patients with moderate and severe pHPT. The effect on PTH is characterized by fluctuations and is apparently dose- and time-dependent since stabilization was achieved following several years of treatment. The steady increase of Vit D3 levels could also have contributed to PTH moderation. These results, though numerically limited, should be considered when long-term medical treatment of pHPT is applied.

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P230

Coexistence of a large functioning parathyroid cyst with papillary thyroid carcinoma: a case report

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Introduction
Parathyroid cysts constitute a rare cause of primary hyperparathyroidism (PHPT). PHPT may also rarely coexist with non-medullary thyroid carcinoma (NMTC).
Case presentation
A 70-year old woman was admitted to our department for type 2 diabetes mellitus (T2DM) management. She also reported nephritic colics due to kidney stone disease. There were no reports for fractures, symptoms of hypercalcemia or obstructive neck symptomatology. Laboratory investigation for nephrolithiasis showed elevated serum total calcium and parathyroid hormone (PTH) concentrations: 10.8 mg/dl (corrected calcium, normal range: 8.4–10.4) and 187 pg/ml (normal range: 10–53). Serum phosphorus, magnesium and 25-hydroxy-vitamin D levels were low: 2.34 mg/dl (normal range: 2.5–4.5), 1.7 mg/dl (normal range 1.9–2.5) and 9 ng/ml (sufficiency levels $>$30), respectively. Renal function was normal (estimated glomerular filtration rate (eGFR): 144.3 ml/min/1.73 m^2), as were the 24-h urinary calcium concentrations 189 mg/24-h (normal range: 50–300). Dual-energy X-ray absorptiometry (DXA) in lumbar spine was indicative of osteopenia (T-score: -2.3). Renal ultrasound was negative for the presence of kidney stones. Primary (PHPT) combined with secondary hyperparathyroidism was diagnosed and the patient underwent a neck ultrasound and parathyroid scintigraphy (Sestamibi) scan, which were indicative of a cystic mass attached to the lower pole of the right thyroid lobe with an estimated maximum diameter of 6.5 cm. Multinodular goitre was also diagnosed with some of the nodules being suspicious for malignancy. The patient underwent an uneventful right parathyroidectomy and total thyroidectomy. Post-operative corrected calcium and PTH levels were 9.3 mg/dl and 17 pg/ml. Histopathological diagnosis was also positive of a unifocal papillary thyroid carcinoma

(PTC) of follicular variant, 6 mm in diameter, without extrathyroidal extension. Due to the patient's low risk of PTC recurrence, no radioiodine was administered. The patient remains normocalcemic (with normal PTH levels and vitamin D sufficiency) and no signs of PTC recurrence two years after.
Conclusions
Functioning parathyroid cysts constitute a rare cause of PHPT. Large parathyroid cysts may be asymptomatic. PTC may rarely coexist with PHPT but it is not known if this is just a diagnosis of coincidence or a result of common pathogenetic mechanisms.

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Assessment of calcium and vitamin D medications adherence in patients with hypoparathyroidism after thyroidectomy

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Aim
In this study, we aimed to evaluate the vitamin D and calcium treatments adherence in patients with hypoparathyroidism after surgery.
Materials and methods
To elucidate the medication adherence, we performed a questionnaire survey using the six item Morisky Medication Adherence Scale for medication of patients with postoperative hypoparathyroidism. These 6 questions were as follows; 1) Do you sometimes have problems remembering to take your medications? 2) Do you pay attention to take medications at exact time? 3) Do you sometimes leave your medication when you feel yourself well? 4) Do you stop sometimes your medication if you feel yourself bad and think that it is associated with medication? 5) Do you know long term benefits of taking your drugs? 6) Do you forget to being prescribed your medications when the prescription time comes? The answers were evaluated as Yes/No. In addition to these six questions, three more questions were added concerning to have worry about side effects of drugs.
Results
Totally 64 patients (12 men, 52 women; median age 48.6 ± 11.6 years) who had postoperative hypoparathyroidism were included in our study. Average duration from diagnosis to evaluation time was 73.0 ± 72.6 months. Average calcium and vitamin D dosages were 1388.39 ± 897.92 mg and 0.61 ± 0.39 μg, respectively. However, in evaluation of calcium usage, motivation level was low in 16 (26.2%) patients and information level was low in 12 (19.7%) patients. Moreover, for vitamin D usage, motivation and information levels were low in 8 (13.3%) and 4 (6.7%) patients, respectively. We found that motivation score of calcium usage was significantly low compared to vitamin D usage ($P<0.001$) Calcium motivation score was found as decreasing significantly with increasing disease time ($r=-0.256$ and $P=0.046$). 38 (59.4%) patients had worry about side effects of calcium treatment. Of these, 10 (15.6%) patients left medication due to this feeling. 55.5% of patients had worry about renal problems such as nephrolithiasis and renal toxicity. 21 (32.8%) of patients declared that they were using lower doses of both drugs than recommended.
Conclusion
In this study, we found that one third of the patients had low motivation for calcium usage and more than half of patients had worry about side effects. We think that these patients must be informed about side effects and convinced about regular and careful follow-up of treatment associated side effects especially in patients who are under calcium treatment.

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Preoperative serumvitamin D levels in patients with breast cancer: association with histological characteristics

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Objective
Vitamin D is a multifunctional hormone with possible antitumor effects. Its exact role in breast carcinogenesis remains largely unknown. We evaluated serum vitamin D levels in female patients with recently identified benign or malignant lesions of the breast and its associations with tumor histology.
Subjects-methods
One hundred sixty women with suspicious breast masses that required surgical excision were included in this study. Body composition data were measured using bioelectrical impedance. Pre-operatively, patients provided early morning blood sample for the quantification of Vitamin D status and other biochemical parameters. Determination of vitamin D status of the patients was implemented by quantification of 25-hydroxyvitamin D3 and D2 metabolites ($25OH\text{-}D_3/D_2$) in serum samples of the patients by our previously developed and validated HPLC-DAD method (1). Surgically excised lesions were sent for histological examination and histopathological characterictics were recorded.
Results
After histological examination of the tumor specimens, 64 specimens were found with benign histology and 96 specimens had malignant characteristics. Comparisons between study groups are shown in Table 1. Cancer patients were older and had greater waist circumference. Vitamin D3 levels were similar in patients with benign lesions vs. those with malignancy. Regarding associations with histological characteristics, Vitamin D3 was associated with nodular metastasis ($\rho=0.26$, $P=0.03$) and Ki67 levels ($\rho=0.27$, $P=0.02$) but did not correlate with tumor size ($\rho=0.06$, $P=0.62$). No significant associations were found with overall TNM staging, presence of estrogen or progesterone receptors and Her-2 protein ($P>0.05$ for all).
Conclusions
Vitamin D was associated with tumor aggressiveness. Its role as a non-invasive biomarker of breast cancer prognosis warrants further investigation in longitudinal studies and/or clinical trials.

Table 1

Variable	Benign Group	Cancer Group	*P*
N	64	96	
Age (years)	51.80 ± 12.21	58.51 ± 11.95	**0.001**
Body Mass Index (kg/m^2)	27.78 ± 5.86	28.98 ± 5.17	0.18
Waist Circumference (cm)	89.62 ± 14.63	93.80 ± 13.10	**0.03**
Hip Circumference (cm)	104.45 ± 12.46	107.00 ± 11.13	0.10
Waist-to-Hip ratio	0.86 ± 0.08	0.88 ± 0.07	0.09
Total body fat (%)	36.93 ± 8.34	39.22 ± 9.57	0.07
Glucose (mg/dl)	100.11 ± 16.99	108.03 ± 26.47	0.09
Total Cholesterol (mg/dl)	255.19 ± 259.71	214.98 ± 41.61	0.14
Triglycerides (mg/dl)	99.61 ± 47.75	109.38 ± 52.24	0.22
Vitamin D_3 (ng/ml)	19.92 ± 9.87	18.94 ± 11.17	0.58

Reference
1. D. Palaiogiannis *et al*. J Chromatogr B Analyt Technol Biomed Life Sci, 1043 (2017) 219-227. PMID:27756628.

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Association of vitamin D status with pulmonary function: potential mediation by physical function and inflammation

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Background
Several studies have reported an association between serum 25-hydroxyvitamin D (25(OH)D) concentrations and pulmonary function in the general population. However, results remain conflicting. In addition, the underlying mechanisms by which vitamin D affects pulmonary function are unknown.
Objective
To assess the relationship of vitamin D status with pulmonary function and whether this relationship is mediated by physical function and/or inflammation. We will also examine potential effect modification of sex and smoking in this relationship.

Methods
We analyzed data from the Longitudinal Aging Study Amsterdam (LASA), an ongoing population-based, prospective cohort study in the Netherlands. Data for this study were obtained from the third cohort (2012/2013). For this study we used data of 551 participants aged between 55 and 65 years, with complete data on serum 25-hydroxyvitamin D (25(OH)D, CRP, IL-6 and pulmonary function tests (Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC). In the regression analyses we corrected for age, sex, BMI, serum creatinine, smoking status, alcohol consumption, educational level, physical activity and season of blood collection. In addition, effect modification of sex and smoking, and mediation by physical performance, IL-6 and CRP was tested.
Results
In men, serum 25(OH)D was associated with pulmonary function: 10 nmol/L higher serum 25(OH)D was associated with 1.01% predicted higher FEV_1 (95%CI: 0.03 to 1.98) and 1.02% predicted higher FVC (95%CI: 0.26 to 1.77). In women no assocation between serum 25(OH)D and FEV_1 (B(95%CI):-0.19 (−1.17 to 0.78)) and FVC (0.12 (−0.74 to 0.97)) was found. No effect modification by smoking was found. Serum 25(OH)D had an indirect effect on FEV_1 through physical performance in women. No mediation effect of physical performance in the relationship between serum 25(OH)D and FVC was seen. In addition, CRP and IL-6 were no mediators in the relationships between serum 25(OH)D and FEV_1 and FVC.
Conclusion
Higher serum vitamin D concentrations were associated with better pulmonary function in men, but not in women. Further studies are needed to elucidate potential mechanisms underlying the difference between men and women.

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P234

Quantification of serum 25-hydroxyvitamin D: a comparison between competitive chemiluminescence immunoassay and mass spectrometry coupled to high performances liquid chromatography

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Serum 25-hydroxy-vitamin D (25OHD) is considered the most reliable marker of vitamin D status. Adequate levels 25OHD of are necessary for pleiotropic effects of vitamin D, either skeletal or extra-skeletal. Traditional assays based on immunoassay often show an unsatisfactory accuracy and sensibility. A valuable alternative is Tandem Mass Spectrometry coupled to High Performances Liquid Chromatography (HPLC-MS-MS), that offers a good quantification accuracy, as the contribution of interfering compounds to the final results is limited. We enrolled 110 consecutive patients with Heart Failure, who underwent comprehensive biohumoral characterization. The analyses of 25OHD by chemiluminescence immunoassay (DiaSorin LIAISON) and HPLC-MS-MS were performed at the same moment from two aliquots of the same stored sample. 25OHD levels with LIAISON were statistically lower than with HPLC-MS-MS (17.6±8.9 ng/ml vs 18.9±9.4, $P<0.0001$). The prevalence of Vitamin D insufficiency (<50 nmol/l or 20 ng/ml) was statistically lower using HPLC-MS-MS compared to LIAISON (59% vs 63%, $P<0.0001$). The same result was found for severe Vitamin D deficiency (<25 nmol/l or 10 ng/ml; 20.9% vs 25.4%=<0.001). A good correlation ($R=0.909$, $R^2=0.824$, $P<0.001$) between 25OHD values measured with LIAISON and with HPLC-MS-MS was found. The inter-assay bias was evaluated by Bland-Altman plots: compared to the HPLC-MS-MS method, LIAISON assay demonstrated a mean relative bias of −6.54% with 95% of limits of agreement (−46.52% to +33.44%). HPLC-MS-MS technology is well correlated to the method currently used (CLIA), avoid overestimation of hypovitaminosis D and is a reliable diagnostic tool for 25OHD measurement.

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Maximal foot force and plantar pressure distribution assessed by Footscan is not affected in asymptomatic primary hyperparathyroidism patients

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Background
Primary hyperparathyroidism (PHPT) is associated with various musculoskeletal complaints. It is difficult to evaluate muscle strength as it is hard to extract objective data due to lack of definite methods for measurement.
Objective
To assess the differences between PHPT patients and healthy controls regarding maximum foot force and plantar pressure distribution by using platform pressure measuring system [Footscan (RSscan)].
Methods
Twenty patients with newly diagnosed PHPT (9 F, 12 M) and 21 healthy controls (13 F, 7 M) were enrolled into the study. Static and dynamic parameters of plantar pressure were recorded using a Footscan pressure plate.
Results
Mean age of the PHPT patients and controls were 45.8±11.3 and 41.3±6.8 (p=NS), respectively. BMI were not different in PHPT patients and healthy controls (29.83±4.6 vs. 27.53±2.7, p=ns). When the measurements of four quadrants on foot (Q) taken into account, Footscan analysis revealed similar distribution of plantar pressure between groups (Q1 24.32%±4.4% vs 23.08%±3.8%, Q2 23.98%±4.3% vs 24.99%±4.51%, Q3 27.28%±5.2% vs 25.98%±5.36%, Q4 24.41%±6.0% vs 25.96%±4.7%). Maximum foot force (MaF) was investigated in ten areas of both feet as standard procedure and no statistically significant difference between groups were observed (MaF left: 1008.34±212.1 N vs 994.71±170.3 N, MaF right: 912.00±226.6 N vs 870.14±127.9 N, P=ns).
Conclusion
According to the present study, the parameters of maximum foot force and plantar pressure computed by using platform pressure measuring system were not different in PHPT patients when compared to healthy controls.

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Primary hyperparathyroidism in Russian Federation: epidemiology according to the online register

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Objective
Primary hyperparathyroidism (PHPT) is one of the most frequently diagnosed endocrine disorders. The Russian Registry of PHPT is an on-line web-based database created in 2016 with the aim to estimate the disease prevalence and improve the quality of health care for such patients in Russian Federation. The Endocrinology Research Centre, Moscow represents The Head organization.
Material and methods
We retrieved retrospective data submitted to the Russian PHPT registry (http://pgpt.clin-reg.ru/) between 2007 and 2017 from 10 geographical regions connected at the moment. The clinical, biochemical, radiological and histopathological characteristics of PHPT patients were analyzed for similarity and variability across the centers. There were registered 1914 patients with different forms of PHPT (hypercalcemic, normocalcemic, sporadic and hereditary cases).
Results
The median age of the all patients at the time of diagnosis (1744 women and 170 men) was 55,6±10 years. The median duration from disease onset till diagnosis was 2 years in Moscow and 5 years in other regions. According to the Registry the sporadic PHPT was the most frequent form and caused by solitary adenoma. The estimated incidence of parathyroid cancer was 2% comparable with other epidemiological studies. PHPT as a MEN syndrome component occurred in 9% of

cases. We included cases confirmed by genetic testing for mutations in the MEN-1 gene (9%) as well as cases with clinical features of MEN 1 syndrome. The most frequent components were pituitary adenoma (30%), adrenal adenoma (27%), pancreatic neoplasm (13,9%). The normocalcemic PHPT with median calcium level 2.45 ± 0.1 mmol/l was observed in 11.7%. The majority of patients were symptomatic (74%). Common clinical manifestations among all PHPT subjects were law trauma fracture and osteoporosis (20% and 8% respectively) nephrolithiasis and/or decrease in glomerular filtration rate (25%), cardiovascular complications (59%), upper gastrointestinal complications (12%). Mean serum calcium, and parathyroid hormone levels in hypercalcemic forms were 2.75 mmol/l ± 0.2 and 250 ± 300 pg/mL respectively. Surgical treatment was performed in 65% cases with recurrence rate 5.1%.

Conclusion

PHPT considerably influences the Russian healthcare system. We observed a tendency to progressive increase in disease detectability. It should be noted that compared to European countries, the symptomatic PHPT is more likely to be diagnosed, which indicates delayed diagnosis because of no routine screening of serum calcium level.

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P237

Intrathyroidal parathyroid carcinoma in a chronic hemodialysis patient: a case report

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Background

Parathyroid carcinoma (PC) is an infrequent pathology, responsible for 0.5–5% of primary hyperparathyroidism cases. Despite the high prevalence of secondary hyperparathyroidism in patients with a chronic kidney disease (CKD), PC among them is extremely rare, with less than 30 cases reported in the literature. The diagnosis of PC in CKD patients is more complex, because of using cinacalcet that reduces the level of calcium and parathyroid hormone (PTH). We report a case of intrathyroidal PC in patients with CKD that was successfully treated by en-bloc resection of the tumor.

Clinical case

A 57-year-old man who had received regular hemodialysis, applied to our center because of uncontrolled hypercalcemia and hyperphosphathemia. He had been treated with cinacalcet 120 mg and sevelamer 4800 mg per day and his laboratory findings were as follows: calcium (Ca) – 2.92 mmol/l (range 2.1–2.55 mmol/l), phosphate (P) – 1.96 mmol/l (0.74- 1.52 mmol/l), PTH – 1983 pg/ml (15-65), alkaline phosphatase – 597 u/l (50-150). Ultrasonography showed an enlarged parathyroid gland (PG) on the right upper side of the thyroid gland with uneven contours of 3.0 x 3.0 x 2.3 cm with calcinate, that was confirmed by CT-scan and 99mTc-Sestamibi scintigraphy. No other PG were identified. During a surgery, intrathyroidal parathyroid tumor was detected that had no clear boundary with the right lobe of the thyroid gland. A locally invasive tumor of the right upper PG and enlargement of the other three parathyroid glands were found during bilateral neck exploration. An en-bloc resection of the upper right PG was performed with the right thyroid lobe, surrounding tissue and paratracheal lymph nodes with subtotal parathyroidectomy of the three enlarged PG. PTH and Ca decreased down after surgery that required taking 2,5 mcg of alfacalcidol and 1,5 g of calcium carbonate per day. Intrathyroidal PC was confirmed by a histological examination that identified vascular and capsular invasion and foci of necrosis. The immunohistochemical study with PTH revealed a positive reaction and confirmed the histogenesis of the tumor from the parathyroid tissue, Ki67 was 5–7%. Three months after surgery the laboratory examination showed: Ca – 2,08 mmol/l, PTH – 117 pg/ml, P – 0.53 mmol/l.

Conclusion

Our case indicates that the use of cinacalcet can hinder the diagnosis of PC in a chronic dialysis patient. When uncontrolled hypercalcemia and/or hyperphosphathemia develop during cinacalcet administration, PC should be suspected, and the appropriate surgery should be planned.

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P238

Raloxifene has no efficacy in reducing the risk of spontaneous vertebral fractures after denosumab discontinuation

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Introduction

Denosumab reduces bone resorption, increases BMD, and reduces fracture risk. Denosumab discontinuation (DD) induces an increase of B-crosslaps above baseline values for two years, and a decrease of BMD values. This rebound effect is associated with spontaneous clinical vertebral fractures (SCVF) in close to 15% of patients considering a follow-up of 2 years without taking another osteoporosis treatment. Prescribing a bisphosphonate or SERMs at DD would prevent the rebound effect and the risk of SCVF.

Case report

A breast cancer was diagnosed in this 60-year-old woman. BMD T-scores were −2.9 DS at the lumbar spine and −1.9 DS at the total hip. The 10-year probability of major osteoporotic fractures assessed by FRAX® was 13%. Letrozole and denosumab were given for 5 years. At the end of the treatment, lumbar spine and total hip BMD increase significantly (+18% and +8%, respectively). Vertebral morphometry confirmed the absence of fractures. Raloxifene 60 mg daily was startet 7 months after DD. B-crosslaps were measured at 33 ng/l (normal range: 25-573 ng/l). Four months later, she experienced spontaneous low back pain. MRI revealed D11 and L5 fractures. B-crosslaps were measured at 2070 ng/l.

Discussion

Raloxifene has not been effective, neither in reducing the high bone turnover, nor in preventing SCVF. In addition, follow-up of B-crosslaps was too much apart. To minimize the high bone turnover at DD, it seems preferable to prescribe a potent bisphosphonate, alendronate or zoledronate. However, frequent measurements of bone turnover should make it possible: 1) to detect the beginning of the rebound effect; 2) to evaluate the effectiveness of the given antiresorptive treatment; and, if necessary, 3) to replace it or to adjust its dosage. However, the threshold value that determines the need for an intervention is unknown. Furthermore, a significant decrease in the high bone turnover after DD is not a guarantee to prevent bone loss and to avoid the risk of SCVF.

Conclusion

Studies are urgently needed to assess the efficacy of bisphosphonates and their optimal doses in such situations.

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P239

Prevalence of basal ganglia calcification in patients with pseudohypoparathyroidism

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Pseudohypoparathyroidism (PHP) is group of heterogeneous disorders characterized by hypocalcemia, hyperphosphatemia and elevated paratormone (PTH) levels as a result of end-organ resistance to PTH. Basal ganglia calcification (BGC) in states of hypoparathyroidism is not uncommon. In PHP, BGC can occur up to 50%; the pathogenesis is poorly defined. The aim of our study was to evaluate the prevalence of BGC at baseline observation in a series of patients with PHP followed at a tertiary center. The diagnosis of PHP was based on clinical features and confirmed by genetic analysis. We evaluated 21 patients with a mean age of 21 ± 12 (7 males and 14 females) with a diagnosis of PHP type I (1A, $n = 5$; 1b, $n = 13$), pseudopseudohypoparathyroidism ($n = 1$). Two patients were

negative at genetic screening. Five (23.8%) subjects had familial PHP type 1A. All patients underwent brain computed tomography (CT, $n=20$) or magnetic resonance imaging (MRI, $n=1$) to detect the presence of BCG. Biochemical and clinical data were available for all patients. BGC were present in 8 (38,1%) patients (7 in PHP type 1b and one in type 1A). 37% were present in males and 62% percent in females, ($P=0.5$). The localization of BCG was pallidum in two patients, all basal ganglia in two, pallidum, cerebellum and caudatum in one, cortical-subcortical junction and caudatum in one, pallidum, striatum and cortical-subcortical junction in one and pallidum and subcortical area in one. Four (19%) patients had other cerebral calcifications, localized in cerebral falx ($n=1$), in pineal gland ($n=1$), choroid plexus ($n=1$) and soft cerebral tissue ($n=1$). Before diagnosis, two of 21 (9.5%) patients presented seizures and one (4.8%) neurocognitive alterations; none of them had BCG. Three patients had soft tissue calcification and two of them also had BCG. Eight patients (38%) presented signs or symptoms of hypocalcemia before the diagnosis, and all but one had BCG. At baseline evaluation, 6 of 21 patients were taking calcium supplements and calcitriol. Mean serum calcium, phosphate and PTH levels were 7.7 ± 1.5 mg/dl, 4.863 ± 1.8 and 440.1 ± 397 pg/ml, respectively. In conclusion, our study finds a high rate of BCG in patients with PHP, with no significant difference between gender. Calcifications were detected in different cerebral sites, usually without clinical manifestations. However, their clinical value is still unclear. Our results suggest evaluating the presence of BCG in PHP and monitoring them with CT o MRI during follow-up.

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P240

Thyroid oncocytes may complicate ^{18}F-fluorocholine PET-CT localization of parathyroid adenomas in primary hyperparathyroidism

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^{18}F-fluorocholine positron emission tomography/X-ray computed tomography (PET-CT) was carried out in our patients with primary hyperparathyroidism (PHPT) and inconclusive preoperative neck ultrasound and ^{99}Tc-sestaMIBI scintigraphy to localize abnormal parathyroid glands before surgery. The results were retrospectively evaluated and compared to postoperative histopathological findings. A total of 9 patients (1 man, 8 women) with sporadic PHPT was enrolled with a mean age of 62,2 years, mean preoperative levels of calcium 2.71 mmol/l and parathyroid hormone 124 ng/l. ^{18}F-fluorocholine PET-CT correctly localized a parathyroid adenoma in 7 patients of 9 (sensitivity 0.77). In one patient, adenoma was successfully found by a surgeon in spite of negative ^{18}F-fluorocholine imaging (false negative). In 2 patients, ^{18}F-fluorocholine PET-CT localized 3-4 foci suggestive of parathyroid hyperplasia and/or multiglandular disease. In one of them, only a single adenoma was found. In the other subject, in spite of bilateral cervical exploration with total thyroidectomy, parathyroid adenoma was not found resulting in persistent hyperparathyroidism (false positive). In the present cohort, positive predictive value of ^{18}F-fluorocholine PET-CT parathyroid imaging was lower than sensitivity due to a few false positive results (0.66). 8 of 9 patients had underlying thyroid disease (thyroid nodules and/or autoimmune thyroid disease). High uptake of ^{18}F-fluorocholine has been documented in oncocytic thyroid adenoma. In all patients (3 of 9) with inconclusive ^{18}F-fluorocholine PET-CT imaging either oncocytic thyroid cells or oncocytic metaplasia were found by aspiration cytology or postoperative histopathology. In our study sample, ^{18}F-fluorocholine PET-CT allowed to correctly localize parathyroid adenomas in 77% patients with previously inconclusive conventional imaging. Underlying thyroid pathology, in particular, thyroid oncocytes, may complicate ^{18}F-fluorocholine PET-CT parathyroid imaging. Further studies are needed to evaluate ^{18}F-fluorocholine PET-CT imaging in patients with PHPT and simultaneous thyroid disease.

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P241

Burden of illness among patients with chronic hypoparathyroidism not adequately controlled with standard therapy by self-perception

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Significant knowledge gaps exist regarding the humanistic effects of chronic hypoparathyroidism (HPT), a rare, debilitating condition. We provide interim results from a global survey conducted to characterise the burden associated with chronic HPT from the patient perspective. An anonymous, self-reported survey (online or paper) was conducted in patients with chronic HPT, not adequately controlled with standard therapy by self-perception, from 12 countries through physicians or patient associations. Symptoms and impact of HPT were assessed via HPT Symptom Diary, a disease-specific, patient-reported outcome tool that recorded severity of symptoms experienced in the last 7 days. Health-related quality of life (HRQoL) was evaluated by 2 validated instruments: SF-36 v2 and EQ-5D-5L. Patient demographics and clinical characteristics were also captured. Data were obtained from 226 patients (mean age, 51.6 years; 77% women; mean time since diagnosis, 7.8 years; surgery as main cause of HPT, 81%), of whom 94% had persistent symptoms despite treatment and 63% had been told by a physician that their calcium levels were poorly controlled. Most patients were receiving oral calcium (77%) and/or activated vitamin D (74%). Self-perceived overall symptom severity was reported as mild, moderate, or severe in 56 (25%), 138 (61%), and 30 (13%) patients, respectively. Per symptom diary, 98% of patients reported physical fatigue (symptom severity: mild, 22%; moderate, 42%; severe, 26%; very severe, 9%), 90% reported muscle cramps (mild, 31%; moderate, 42%; severe, 13%; very severe, 4%), and 90% reported heaviness in limbs (mild, 24%; moderate, 46%; severe, 16%; very severe, 4%). An impact on daily life, rated as 'somewhat' or 'very much', was reported by 89% of patients for ability to exercise, 85% for sleep, 80% for ability to work, and 72% for family relationships. An apparent inverse relationship was observed between scores of HPT symptom severity and both HRQoL assessments – the higher the severity scores, the lower the health status. Mean SF-36 summary scores were 44.3/36.6/28.2 (physical component summary) and 44.4/33.9/31.4 (mental health component summary) for patients reporting mild/moderate/severe HPT symptoms, respectively. Mean EQ-5D scores were 0.8/0.7/0.3 for patients reporting mild/moderate/severe HPT symptoms [$n=132$]). Findings from this interim analysis of a global survey demonstrated that there is a spectrum of symptom severity within a cohort of patients self-reporting inadequately-controlled HPT on standard therapy. The magnitude of symptom severity as reported by patients correlated with extent of impact on daily life and reduction in HRQoL.

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P242

Abstract withdrawn.

P243

PTH secretion dynamics in patients with chronic kidney disease stage 3 and stage 4 during 1 year of observation

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Secondary hyperparathyroidism (SHPT) is common in patients with chronic kidney disease (CKD). The aim of the study was to analyze dynamics of PTH secretion during 1 year of observation of patients with CKD stage 3 and 4. We examined 40 patients, 22 f, 18 m; age 55.9 ± 14.5 years. Mean glomerular filtration rate (GFR)? Calculated by MDRD formula was 27.2 ± 15.7 ml/min; 15 patients have CKD stage 3, 25 – stage 4. Serum PTH, 25(OH)D3, calcium (Ca) and phosphorus (P) were measured initially and at the end of observation period (mean 12.4 ± 1.6 months). Initially SHPT as well as vitamin D deficiency were revealed in 80% of cases. 90% of patients with vitamin D deficiency had SHPT. We found significant negative correlation of PTH level and eGFR ($r = -0.55$), vitamin D level ($r = -0.34$). 20 patients with vitamin D deficiency (25(OH)D3 $<$20 ng/ml) were recommended to receive vitamin D supplements, 2000 IU daily. After 1 year PTH increased in 45% of patients, mean increase was 65.4 pg/ml (95%CI 27.5 – 103.3). Subgroup with increased PTH shown higher initial PTH level ($P = 0.003$) and lower eGFR ($P = 0.0008$). At the end of observation we did not found significant changes of PTH level both in patients received vitamin D and not received supplements. PTH was 168.5 ± 132.1 initially and 164.7 ± 1.6 pg/ml at the end of observation, $P = 0.578$. GFR significantly declined from 27.2 ± 15.7 to 21.3 ± 1.8 ml/min ($P = 0.0004$). At the same time in patients received vitamin D supplements vitamin D level increased from 11.6 ± 5.0 to 31.1 ± 12.3 ng/ml, $P = 0.0002$, Ca and P levels remained unchanged. In the subgroup of patients not supplemented with vitamin D serum Ca decrease from 2.46 ± 0.19 to 2.35 ± 0.15 mmol/l. We can assume that in patients with CKD stages 3 and 4 frequency of both SHPT and vitamin D deficiency is high (80%). Supplementation of vitamin D 2000 IU daily allows restoring normal vitamin D level but seems to not have significant effect on PTH, at list on its decrease. 45% of patients demonstrate PTH increase after 1 year of observation, most predictive value have initial higher level of PTH and lower GFR. Further study is required to confirm this findings and to choose the best strategy of follow-up for patients with SHPT.

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P244

Biological and endocrine features of Infra Clinical Hypoparathyroidism in Major Beta Thalassemia at adulthood in Algeria, screening and therapeutic management

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Introduction
Major Beta Thalassemia (MBT) is a common hereditary condition in Algeria (2%) and in North Africa it requires repeated transfusions. Life expectancy has improved significantly thanks to advances in chelating treatments that will delay endocrine complications associated with secondary hemochromatosis. The hypoparathyroidism (HPT) continues to be seen (5–20%), its relation with the iron overload is not clearly elucidated.
Patients and methods
It is about 20 BTM patients of mean age 29 years (20–46) (10 Males/10 Females) hospitalized in hematology at the Pierre Marie Curie Center, Algiers. In whom an infra-clinical HPT has been researched in cases of hypocalcemia, hyper-phosphoremia or high alkaline phosphatase.
Results
The prevalence of asymptomatic HPT is 25%, normo-calcemic in 40%. Vitamin D $<$ 10 ng/ml exists in 50% of MBT. Among patient with HPT, 3 patients are diabetics. 2 patients had infra clinical hypothyroidism, only one BTM with HPT has a growth delay less than 2 deviation, and all cases have central hypogonadism except one patient. All HPT patients are under Defirasirox, the 5 cases benefited from biological check up of magnesium level and bone densitometry.
Discussion
An **annual screening** of HPT after the start of the second decade is required. Its coexistence with a frequent **hyper-calciuria** in the BTM make that the conventional preventive treatment by living D and calcium in the long course must be reviewed because of the risk of nephrocalcinose worsening the renal prognosis already altered by the renal hemosiderosis. Other therapeutic weapons such as **recombinant Parathormon** prove to be more effective both renally and on bone capital already altered by other endocrinopathies such as central hypogonadism. Exception for infra clinical HPT, in which "**wait and see**" seems to be more adequate management.

Patients	Age (years)/Sex	Calcium/ phosphorus	PAL ui/l	Parathormon pg/ml	Vit D ng/ml	Feritin ng/ml
Case 1	25/Female (F)	**84**/43 mg/l (miligrams/liter)	106	15.41	8.2	9177
Case 2	35/Male (M)	69/42 mg/l	144	16.07	8.1	1500
Case 3	26/F	57/81 mg/l	113	4.81	8.1	8620
Case 4	31/M	77/48 mg/l	Not available	22.34	12.9	5736
Case 5	28/M	**86**/54 mg/l	170	22.77	8.1	4193

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P245

Impact of vitamin D status in clinical, biochemical, radiological and pathological parameters in primary hyperparathyroidism

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To determine the effects of 25-hydroxyvitamin D (25-OHD) status on parathyroid adenoma weight, clinical, radiological and biochemical phenotype in patients with primary hyperparathyroidism (HPTP) were studied.
Methods
Eighty-two patients with pHPT who underwent surgical treatment and in whom the presence of parathyroid adenoma were confirmed histopathologically were studied retrospectively. Patients were divided into 2 groups: group A patients with 25-OHD concentrations $<$ 20 ng/ml ($n = 49$) and group B patients with 25-OHD concentrations $\geq$ 20 ng/ml ($n = 33$). Serum parathyroid hormone (PTH), albumin-corrected serum calcium, phosphate, alkaline phosphatase and urinary calcium excretion were determined. The results of preoperative imaging modalities (ultrasound, planar scintigraphy and SPECT/CT) and parathyroid adenoma weight were recorded.
Results
74% of patients presented vitamin D insufficiency ($<$ 20 ng/dl). No statistically significant differences were observed with respect to serum calcium, phosphorus, PTH, alkaline phosphatase concentrations, urinary calcium excretion and parathyroid adenoma weight between groups. The history of bone fracture was more frequent in group A (9.7% vs 1.2% $P = 0.03$). Likewise, group A presented lower values of bone mineral density at femoral site, although it did not reach statistical significance (0.67 vs 0.73, $P = 0.07$). Significant correlations were observed between 25 OHD and femoral mineral density ($r = 0.331$, $P = 0.01$), and serum PTH ($r = -0.233$, $P = 0.03$). Parathyroid adenoma weight correlated with serum calcium ($r = 0.404$, $P < 0.001$), serum phosphate ($r = -0.243$, $P = 0.03$), and PTH ($r = 0.523$, $P < 0.001$). No biochemical/pathological features were suggested to influence in the localization studies.
Conclusions
Vitamin D deficiency is a common disorder in patients with HPTP. It seems to lead to more severe bone disease. Our results suggest that there is not an effect of vitamin D deficiency on parathyroid tumor growth.

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P246

Milk alkali syndrome & soft tissue calcification in a patient with a history of cancer

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A 61-year-old female, with a previous history of left nephrectomy for papillary renal cell carcinoma, presented with lethargy. Her initial blood tests revealed an

adjusted calcium of 4.26 mmol/l (normal range 2.2–2.6) associated with acute renal impairment (creatinine 432 μmol/l, urea 25 mmol/l) and low PTH of 9 ng/l (normal range 20–75). Following rehydration with IV fluids and IV pamidronate administration, her adjusted calcium normalised to 2.37 mmol/l. The initial impression was that her hypercalcaemia was most likely malignancy related. Imaging including CXR, renal US, CT scan of thorax, abdomen, pelvis and MRI brain and whole spine were all unremarkable. A bone isotope scan revealed abnormal increased uptake over both hemithoraces suggestive of soft tissue calcification. On further questioning, it appeared that the patient had been taking a full packet (36 tablets) of Setlers antacid (calcium carbonate 500 mg per tablet) per day for the previous 6 weeks for indigestion indicating her hypercalcaemia was due to Milk Alkali Syndrome. The medication was stopped. Three months later, a repeat bone isotope scan, showed that the increased uptake over the right hemithorax had resolved with reduced intensity over the left hemithorax. Several months later her calcium levels remained normal. About 90% of cases of hypercalcaemia are caused by primary hyperparathyroidism or malignancy, however, this case illustrates the importance of considering less common causes of hypercalcaemia even in a patient with a history of cancer.

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P247

Management of parathyroid adenomas

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Introduction

Preoperative localization of parathyroid adenomas still remains a problem, despite advances in imaging of the parathyroid gland. The purpose of our presentation was to present our attitude in the diagnosis and the treatment of parathyroid adenomas and in case of recurrence.

Method

Our study includes 33 cases of primary hyperparathyroidism treated in our department, during a period of 15 years (2002–2017). All patients were referred from the endocrinology department after the biological diagnosis was made and the surgical indication was discussed.

Results

The average age was 55 years old with extremes of 20–80. They were 24 women and 9 men. Patients presented with complaint of asthenia, polyuria, polydipsia associated with bone pain in 17 cases. All our patients were systematically explored by cervical ultrasonography, Thallium-Technetium scintigraphy in two cases and 99Tc-sestamibi in 31 cases. The preoperative localization of the adenoma was done in 28 cases. 99Tc-sestamimbi scintigraphy revealed parathyroid hypertrophy in 26 patients and perfectly localized them. Thallium-Tc scintigraphy was helpful in one patient, while it missed a 15 mm right superior adenoma in another patient. Cervical ultrasonography showed same result with surgery in 21 patients. Cervico mediastinal CT scan was performed in five cases and MRI in one case. Peroperatively, double localization was noted in two patients. The efficiency of surgery was confirmed by a postoperative parathyroid hormone level monitoring. Surgical revision was necessary in three cases, for persistence of elevated parathyroid hormons levels (In one case it was a 1.2 cm adenoma found in left retrovascular position, in the second case it was a 0.8 cm adenoma localized in the the tracheoesophageal groove and the last case it was an intrathymic 1.5 cm adenoma). Postoperatively, a case of chondrocalcinosis was noted in one patient, severe hypocalcemia at 1.7 mmol/l was noted in a patient with a tetany crisis.

Conclusion

In terms of parathyroid adenomas, a well detailed preoperative imaging done by an experienced radiologist is of great help for the surgeon but does not necessarily lead to a better success rate compared to conventional bilateral neck surgical exploration.

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P248

Recurrent hyperparathyroidism: parathyroid carcinoma or parathyromatosis?

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Recurrent hyperparathyroidism (HPT) refers to reappearance of hypercalcemia after a normocalcemic period of at least 6 months post-parathyroidectomy. Parathyroid carcinoma is a rare cause of primary hyperparathyroidism (pHPT), accounting for 0.4–5.2% of cases. Parathyromatosis is defined as small nodules of hyperfunctioning parathyroid tissue scattered in the soft tissues of the neck and/or mediastinum. We describe two cases with recurrent hypercalcemia after surgical interventions for pHPT.

Case 1: A male patient, MI, 47 yo, had recurrent hypercalcemia despite three parathyroidectomies. At first presentation, his labs were Ca = 15.4 mg/dl, PTH = 340 pg/ml. Sestamibi parathyroid scintigraphy and MRI scan of the neck showed an upper left parathyroid adenoma. It was removed in 2012 and pathology was consistent with adenoma. He remained normocalcemic for 3 years, and then his hypercalcemia recurred. The patient underwent surgery for the second time, when unfortunately the recurrent left nerve was accidentally cut. In November 2016, he underwent a third surgical neck exploration and pathology indicated a parathyroid carcinoma. Postoperatively, the calcium was within the normal range for 3 months. At the last evaluation in 2017, Ca = 12.3 mg/dl, PTH = 219.5 pg/ml (NR:7.5–53.5). MRI scan showed two nodules: one located left paratracheal area and one behind the left sternocleidomastoid muscle. He began medical management with alendronate and the fourth surgery was scheduled.

Case 2: A male patient, IB, 45 yo, was admitted in our Clinic in May 2017, due to recurrent hyperparathyroidism. Laboratory data when patient was diagnosed with pHPT for the first time indicated Ca = 14.4 mg/dl, PTH = 2000 pg/ml due to a lower left parathyroid adenoma. He was operated in 2012 and adenoma was confirmed by pathology. After 5 years he presents with: Ca = 16.7 mg/dl, PTH = 5000 pg/ml (NR:12–65). Sestamibi parathyroid scintigraphy and ultrasound exam showed recurrence. He underwent surgery for the second time and pathology indicated a parathyroid carcinoma. Both patients were males, with benign disease after first surgery and without any renal disease. None of them presented local or distant metastasis. Regarding the origin of parathyromatosis there are three theories we took into account: it is a low-grade parathyroid malignancy, it results from seeding of the parathyroid tissue during surgery for pHPT or it is an overgrowth of an embryologic rest. In conclusion, in some cases, it should make a distinction between a locoregional metastatic parathyroid carcinoma with multiple implants and paratyromatosis.

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Prenatal hypophosphatasia with severe skull bone deficits report of a case

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Hypophosphatasia (HPP) is a rare inherited disorder caused by loss-of-function mutations in the tissue-nonspecific alkaline phosphatase (TNSALP) gene. HPP B is a multisystemic B disorder with a predominantly B skeletal phenotype, with a clinical spectrum ranging from high lethality in early onset (< 6 months) HPP to mild late-onset presentations. HPP skeletal disease in utero was thought to predict a lethal outcome. However a benign prenatal form (PB HPP) with a mild postnatal course has been emphasized in several reports. We report the case of a girl born full term with absent parietal bones, severe deficits in temporal and occipital bones and widely separated frontal and lambdoid sutures. There was also absence of the nasal bone and severe hypoplasia of the clavicles. No respiratory support was required. The laboratory investigation revealed low levels of ALP (44 U/L-77 U/L, ref. range 115–460 U/L) with normal levels of calcium and phosphorus in blood and urine, normal serum magnesium, PTH and 25(OH) D levels. The TNSALP gene was analyzed by PCR and direct sequencing. A heterozygous TNSALP variant c.542C > T was detected, which has been predicted as pathogenic and has been identified in compound heterozygosity in two cases of infantile HPP and in heterozygosity in a patient with adultHPP. On re-evaluation 6 months later, there is no improvement of her bone deficits, with persistently low alkaline phosphatase and calcium levels at the upper normal range. In light of this clinical course, Asfotase alfa has been considered as a possible treatment due to the persistence of extended skull deficits.

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P250

Clinical outcome in primary hyperparathyroidism: A 10-year tertiary care centre experience in Pakistan

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Background
Primary hyperparathyroidism (PHPT) is characterized by abnormal regulation of PTH secretion by calcium. The most common clinical presentation of PHPT is asymptomatic (80% cases), followed less likely by the classical symptoms of bones, stones, abdominal moans, and psychic groans. The diagnosis of PHPT is usually first suspected because of the finding of an elevated serum calcium concentration along with a rise in Parathyroid hormone (PTH) level. Serum phosphorus levels are usually normal to high in patients with PHPT. These investigations are then followed by the localization studies such as Ultrasound Neck, Sestamibi scan or CT/MRI scan. Parathyroid adenoma resection is the only definitive treatment to cure the disease.
Objectives
This study was designed primarily for the evaluation of diagnostic characteristics and management outcomes of PHPT over a span of 10 years at a tertiary care hospital in Pakistan.
Methods
It was a Descriptive cohort study. Total 55 patients with biochemical and radiological diagnosis of PHPT were included in study between January, 2007 to December, 2016. Patients' medical record files were reviewed & data recorded.
Results
Of the 55 subjects, with mean age of 39.68 ± 14.35 years, 44 (80%) were females while 11 (20%) were males. The patients presented at a mean duration of 1.20 ± 3.12 years after onset of symptoms. The most frequent complaint was joint & bone pains noted by 49 (89.1%) pts. SestaMIBI scan proved the culprit lesion to be on the right side of neck in 24 (43.6%) pts, left side in 22 (40%) pts and bilateral in 7 (12.8%) pts. Overall, 40 (72.7%) patients underwent surgical resection of parathyroid adenoma, out of which 33 (82.5%) achieved remission while the rest had to undergo repeat surgery to achieve remission. Fifteen (27.3%) patients refused to opt surgical option, thus not achieving remission. Alendronate was the most commonly adopted medical treatment.
Conclusion
To the best of our knowledge, this important endocrinal entity of PHPT had never been studied in Pakistan in terms of estimating the prevalence of its clinical profile, understanding the diagnostic characteristics in our set-up and observing the management outcome. PHPT most commonly presents with skeletal manifestations (80.1%) in our area. Surgical adenoma resection is followed by the documentation of remission in 82.5% pts. With the continuously improving surgical skills, we expect that the figures attaining remission after primary surgical resection will rise in the decades to come.

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P251

Primary hyperparathyroidism-localisation studies' sensitivity

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Primary hyperparathyroidism can be caused by adenoma, adenocarcinoma, parathyroid hyperplasia or ectopic parathyroid glands. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism recommends imaging as a helping tool in locating the causative lesion rather than a must for diagnosis. Experienced surgeons rely on the intraoperative localisation of the lesion. Pre surgery localisation helps for a minimally invasive approach. Technetium sestamibi scintigraphy, cervical-mediastinal CT and cervical region ultrasound are the most frequent used techniques but their sensitivity and specificity differs. In our center surgeons appreciate a pre-surgery localisation. We present the results of a retrospective pre surgery localisation study, conducted in C.I Parhon National Institute of Endocrinology, Bucharest, which enrolled 466 subjects with primary hyperparathyroidism, hospitalized between 01.08.2015 and 31.07.2017. Anterior cervical region ultrasound was performed to all subjects, 33% underwent scintigraphy, and 60% were CT scanned. In our hospital, sensitivity for cervical ultrasound was 59%, 50% for technetium scintigraphy and 76% for CT. In conclusion, we use at least two pre surgery localisation imaging technique. The most frequently used one is ultrasound doubled either by cervical CT or scintigraphy. Choosing the second imaging technique depends of the expertize of the center.

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P252

Characterization of the parathyroid hormone requests and hyperparathyroidism etiologies in a tertiary hospital

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Introduction
Hyperparathyroidism is a disease characterized by excessive secretion of parathyroid hormone (PTH). There are three main etiologies: primary (PHPT), secondary (SHPT) and tertiary hyperparathyroidism (THPT). PHPT is characterized by abnormal regulation of PTH secretion by calcium, resulting in hypersecretion of PTH relative to the serum calcium concentration. SHPT is the overproduction of PTH in context of hypocalcemia, most frequently because of vitamin D deficiency and/or chronic kidney disease (CKD). THPT is a state of excessive secretion of PTH after longstanding SHPT and resulting in hypercalcemia.
Objectives
To evaluate the PTH requests and the causes of hyperparathyroidism in a central hospital.
Methods
Retrospective study of PTH measurements and corresponding patients' records performed between May 2016 and June 2017. Hyperparathyroidism was defined as PTH >72 pg/ml, determined by electrochemiluminescence immunoassay. CKD was established according to the Kidney Disease Outcomes Quality Initiative guidelines. Statistical analysis was performed with SPSS software, version 20.
Results
A total of 1085 PTH measurements were recorded, corresponding to 955 patients. Of these, 349 had hyperparathyroidism. Excluding patients with insufficient clinical information ($n=22$), there were 327 patients (62.1% female; 68.7 ± 0.9 years), with the following diagnosis: PHPT, $n=28$ (78.6% female, 64 ± 2.6 years); SHPT $n=296$ (60.5% female, 69.4 ± 1 years), THPT $n=2$ (100% female, 42.5 ± 17.5 years) and 1 case of familial hypocalciuric hypercalcemia (male, 49-year-old). The causes of SHPT were: chronic kidney disease (CKD, 122); vitamin D deficiency (107); combined CKD and vitamin D deficiency (64); Paget's disease (2) and pseudohypoparathyroidism (1). Patients with CKD (186) presented the following distribution: stage 3, $n=69$; stage 4, $n=63$ and stage 5, $n=54$. In the patients with hyperparathyroidism, the PTH measurement was requested by different departments: Internal medicine (127), Nephrology (69), Rheumatology (38), Endocrinology (38), Haematology (13), Infectious diseases (10), Pneumology (9), Gastroenterology (4), Neurology (4), Cardiology (4), Gynaecology (3), Oncology (3), Surgery (3) and Urology (2).
Conclusions
SHPT was the most prevalent etiology of hyperparathyroidism, particularly the one secondary to CKD, as expected because of the high prevalence of CKD in general population. Different medical specialties requested the measurement of PTH. Probably, in our institution, this is a laboratory test excessively requested, increasing medical costs without benefits for the patients.

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P253

Tertiary hyperparathyroidism associated with prolactinoma – case report

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Introduction
Tertiary hyperparathyroidism (HPT) occurs most commonly in the setting of renal transplant where patients with secondary HPT continue to have elevated PTH levels after receiving a renal allograft. This disease is observed in up to 30%

of kidney transplant recipients. This paper will include a case report and a review of epidemiology and pathophysiology, complications and clinical findings, indications for treatment, and the drugs currently available to treat this condition.
Case report
The 35-years-old woman with a kidney transplant history (2006), subsequently with kidney graft rejection (2014), hemodialysis for 3 years, has addressed to our department in March 2017 for amenorrhea – galactorrhea syndrome (last menstrual cycle 10 years ago). The serum levels of TSH was slightly elevated (8.8 UI/l) with normal FT4, prolactin was 263 ng/ml and FSH, LH, Estradiol, IGF1, basal Cortisol at 8 a.m. were normal. The evaluation of phospho-calcic metabolism emphasized normocalcemia, hyperphosphatemia with elevated intact PTH levels (1050 pg/ml), normal serum levels of 25-hydroxy vitamin D (30 ng/ml) and increased levels of alkaline phosphatase (772 U/L). An ultrasound scan of the neck showed the hyperplasia of three parathyroid glands. 99mTc sestamibi scintigraphy was negative. Bone densitometry (DEXA L1-L4) revealed osteopenia. Pituitary MRI has described a microadenoma. Medical treatment was initiated with Cabergoline and subtotal parathyroidectomy was recommended. Long term follow-up is required for monitoring related complications.
Keywords: tertiary hyperparathyroidism, prolactinoma, subtotal parathyroidectomy.
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Effect of bariatric surgery on free vitamin D3 levels

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Total vitamin D levels are decreased in obese patients probably due to an increased volume of distribution mechanism. Recently introduced direct assays allow the measurement of free-vitaminD3 levels (fvitD3). Few data are available regarding fvitD3 levels in obese people and the effect of bariatric surgery upon its circulating concentration. We aimed to evaluate fvitD3 in a cohort of obese patients before and after bariatric surgery treatment and its relationship to phosphocalcic parameters.
Methods
Retrospective study including 24 patients (48 y, 20 women, initial weight of 124.66 ± 30.76 kg, waist 131.65 ± 14.19 cm and BMI 48.16 ± 10.73 kg/m^2) treated with sleeve gastrectomy. All patients received standard supplementation with daily 800IU of colecalciferol p.o. after surgical procedure. Evaluation was done before and one year after the intervention and samples for measurement were collected during summertime period. Data regarding body weight, BMI, waist, lipid profile, albumin-corrected calcium, phosphate, PTH, 25-OH-vitaminD and fVitD3 was recorded before and after surgery.
Results
Before surgery, 25-OH-vitaminD in obese patients was 22.08 ± 11.54 ng/ml and fvitD3 was 5.28 ± 2.29 pg/ml; 25-OH-vitaminD and fvitD3 levels showed a positive correlation between them ($r_s = 0.7$, $P < 0.0001$). 25-OH-vitaminD showed an inverse correlation with PTH levels ($r_s = -0.46$, $P < 0.04$) but there was no correlation with fvitD3. Neither 25-OH-vitaminD, nor fvitD3 correlated with weight or BMI before surgery. One year after bariatric surgery (waist 102.64 ± 15.41 cm, BMI 34.82 ± 9.0 kg/m^2), mean 25-OH-vitaminD was 27.31 ± 11.83 ng/ml (p = n.s vs pre-surgery) and fvitD3 increased to 6.64 ± 2.25 pg/ml ($P = 0.03$ vs pre-surgery). There was no statistical correlation between the percent change of fvitD3 and the magnitude of weight loss although absolute concentrations of fvitD3 and 25-OH-vitaminD were inversely correlated with final weight ($r_s = -0.60$, $P = 0.002$ and $r_s = -0.46$, $P = 0.02$ respectively).
Conclusion
fvitD3 is correlated with 25-OH-vitaminD either, pre and post bariatric surgery in morbidly obese patients and it increases 1 year after surgical procedure. Weight and both 25-OH-vitaminD and fvitD3, reestablished a negative correlation after surgery, being the last one of higher magnitude in coincidence with its increased circulating concentrations in the follow up period. This finding may be related with a postsurgical reduction of the kidnaping effect of adipose tissue and affects preferentially the free form rather the total vitD.
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Utility of contrast-enhanced ultrasound in preoperative evaluation of primary hyperparathyroidism

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Purpose
The aim of this study was to evaluate the sensitivy of contrast-enhanced ultrasound (CEUS) in the detection of pathological parathyroid gland in patients with primary hyperparathyroidism in comparison to the 99m-MIBI-SPECT scintigraphy.
Methods
29 patients consecutive (22 female, 7 male) with biochemically confirmed primary hyperparathyroidism, who underwent preoperative imaging with Technetium 99m-MIBI-SPECT scintigraphy and CEUS and subsequent successful parathyroidectomy over a 4 year period were reviewed. All patients were investigated by the same radiologist who was blinded to the result of the scintigraphy.
Results
On pathologic examination, 31 abnormal glands were confirmed. All the glands were adenomatous. CEUS revealed a sensitivity of 62.1% (95% CI 42.3–79.3) for detection of single-gland disease in comparison to 72.4% (95% CI 52.7–87.3) for 99m-MIBI-SPECT scintigraphy. Moreover using CEUS, double adenomas could be detectect in 1 of 2 cases. Alll patients showed normal serum levels of calcium and parathyroid hormone serum levels 3 months after parathyroidectomy.
Conclusion
In our study, CEUS does not replace scintigraphy in localization of pathological parathyroid glands in patients with primary hyperparathyroidism.
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P256

In situ preservation of parathyroid glands in thyroid surgery for prevention of hypoparathyroidism

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Introduction
Hypoparathyroidism (HPT) is one of the most frequent and severe complications of thyroid surgery. It is caused by intraoperative damage, devascularization or accidental removal of the parathyroid glands (PTG). The incidence of postoperative HPT is directly proportional to surgery extent and surgeon's experience. However, it can be significantly reduced by excellent surgical technique. The authors present original technique of *in situ* preservation of PTGs during thyroid surgery and 40-years-experience results in postoperative HPT.
Methods
Dzodic's original surgical technique (personal *PhD thesis*, 1993; published in *J BUON*, 2017) focuses on meticulous capsular dissection and ligation of blood vessels close to thyroid capsule. The key step is preservation of the middle thyroid, Kocher's, vein trunk, as well as vein branches that accompany posterior branch of superior thyroid artery and inferior thyroid artery trunk. The use of methylene blue dye for sentinel lymph nodes biopsy facilitates identification of PTGs during removal of thyroid gland, as well as central neck dissection (in case of thyroid carcinomas), since PTGs are not colored in blue, unlike central lymph nodes.
Results
After 40 years of experience in thyroid surgery, and several thousands of preserved PTGs using *Dzodic's original surgical technique*, a total prevalence of permanent HPT in the personal series is less than 0.5%.
Conclusions
Dzodic's original surgical technique of venous trunk's preservation, along with so far known surgical steps for *in situ* preservation of PTGs on arterial pedicles, provides good outcome for patients after total thyroidectomy, with or without central neck dissection, regarding HPT as one of the most severe complications of thyroid surgery. We find methylene blue dye of great importance, not only for sentinel lymph nodes biopsy, but also for avoiding accidental removal of unrecognized PTGs.
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Primary hyperparathyroidism after thyroid surgery and autotransplantion of parathyroid gland

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Introduction
Multiple endocrine neoplasia type 2A syndrome (MEN 2A) is caused by a germline mutation in the RET proto-oncogene and its phenotype includes medullary thyroid cancer, pheochromocytoma and primary hyperparathyroidism (PHPT). Parathyroid reimplantation in the sternocleidomastoid muscle or in the brachioradial muscle can be performed in case of intraoperative lesion of the parathyroid glands. In some cases, PHPT may occur due to the proliferation of autotransplanted parathyroid tissue, which may hinder its diagnosis.
Case report
Female patient, 55 years old, with personal and family history of MEN2A, with medullary thyroid carcinoma, but no evidence of pheochromocytoma or PHPT. She underwent total thyroidectomy for medullary thyroid carcinoma and remained under surveillance and in remission for 20 years (levels of calcitonin, PTH, serum calcium and plasma metanephrines within the normal range). Afterwards, she developed PTH-dependent hypercalcemia, with serum calcium of 11.1 mg/dl (8.6–10.5 mg/dl), PTH 194.3 pg/ml (12–67 pg/ml) and 24 h urine calcium of 430 mg (80–300 mg). A cervical ultrasound was performed, which showed a 20 mm nodule, anterior to the right sternocleidomastoid muscle and a parathyroid scintigraphy, which described a moderate uptake in the right lateral cervical region, raising questions regarding its etiology. We reviewed the patients' medical charts and found out that the surgical team performed an autotransplantation of the right lower parathyroid in the sternocleidomastoid muscle at the same time of the thyroidectomy, due to likely intraoperative lesion of the parathyroid glands. We decided to perform a fine needle aspiration biopsy of the nodule, which was compatible with parathyroid tissue and PTH measurement in needle washout, which was 33 363 pg/mL. She underwent parathyroidectomy and the histological report was compatible with parathyroid adenoma. The patient is currently in remission, with serum calcium of 8.8 mg/dl and PTH 63.6 pg/ml.
Discussion
Patients with MEN2A who develop PHPT after thyroidectomy and parathyroid gland autotransplantation might be a diagnostic challenge. At reoperation, only enlarged parathyroid glands should be excised. This is a rare case that highlights the importance of clinical evaluation and preoperative localization imaging tests as well as long-term surveillaince of serum calcium and PTH levels.

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Metabolic encephalopathy following intravenous zolendronate for hypercalcaemia of malignancy: a perfect storm

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A 56 year old lady was diagnosed with cancer of unknown primary after the discovery of liver metastases. Prior to the commencement of EOX chemotherapy (epirubicin, oxaliplatin and capecitabine) she was given a dose of 4 mg zolendronic acid for hypercalcaemia of malignancy. Three weeks later she presented to our hospital with a history of rapid decline and reduced oral intake, with associated diarrhoea. She had reduced GCS and hypotension. Initial investigations revealed an acute kidney injury (Ur 74.4 mmol/l, Cr 461 umol/l) with normal potassium, severe hypocalcaemia at 1.10 mmol/l (adjusted) and magnesium 0.41 mmol/l (0.5–0.8). Electrocardiogram showed severe QTc prolongation at 587ms. She was managed on intensive care with intravenous antibiotics, fluids and electrolyte replacement. PTH was appropriately elevated at 32.8 pmol/l (1.5–7.6) with Vitamin D 27 nmol/l. Despite improving metabolic status her GCS remained persistently low; subsequent investigations revealed a normal MRI brain scan, lumbar puncture and paraneoplastic antibiotics. She was diagnosed with metabolic encephalopathy secondary to hypocalcaemia; over a period of four weeks she gradually improved with continued electrolyte correction. Hypercalcaemia of malignancy is found in up to 44% of patients with malignancy, with a number of potential mechanisms involved. Intravenous fluids and bisphosphonates remain amongst the mainstays of treatment. Hypocalcaemia is a recognised complication of zolendronate therapy, with trials suggesting up to 1% of patients may develop a significantly low calcium. The development of renal failure is both a potential complication of this treatment as well as a potentiator of it. Our case illustrates the rare occurrence of metabolic encephalopathy as a consequence of zolendronic acid treatment, risk factors of hypocalcaemia as well as highlighting the importance of giving appropriate education and arranging robust follow-up when patients treated with intravenous bisphosphonates are discharged.

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P259

Primary hyperparathyroidism: a rare cause of hypertension?

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Backgroud
Primary hyperparathyroidism is the most common cause of hypercalcemia, which is associated with an increased frequency of hypertension. However, there are no data on the prevalence of primary hyperparathyroidism in patients who present with hypertension.
Clinical case
We present the case of a 40-year-old woman with a history of hypertension for ten years. In 2017 she was referred for evaluation of hypercalcemia. The patient denied any symptoms related to hypercalcemia. Laboratory testing revealed calcium 2.77 mmol/l (Ref. 2.09–2.42), phosphate 0.64 mmol/l (Ref. 0.87–1.45), parathormone *(*PTH) 121.5 pg/ml (Ref. 15–65), creatinine 0.78 mg/dl (Ref. 0.5–0.9) and vitamin D 72 nmol/l. The patient had no evidence of renal lithiasis on renal ultrasound. Bone densitometry was normal. Although cervical ultrasound was normal, sestamibi scan revealed a left retrosternal lesion, suggestive of a parathyroid adenoma. A CT scan of the neck confirmed a suprasternal oval expansive lesion, in the anterior and superior mediastinum, with 21×11 mm, suggestive of an ectopic parathyroid adenoma. The patient denied family history of hypercalcemia. She is waiting for parathyroid surgery.
Conclusion
Most patients with primary hyperparathyroidism are asymptomatic, but others may present with symptoms related to chronic hypercalcemia, such as hypertension. Hypertension may or may not remit after successful parathyroidectomy. We will follow this patient to evaluate hypertension remission.

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P260

Atypical Parathyroid adenoma in a young individual, presented with nephrocalcinosis

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Introduction
Primary hyperparathyroidism (PHPT) is a rare disorder among young adults. Classic manifestations of PHPT, such as nephrocalcinosis, nephrolithiasis, are rarely seen today.
Case report
We refer the case of a young male, 25 years old, presented in emergency unit with: headaches, lumbago, epigastric pain, weight loss (5 kg during six last months), polydipsia-polyuria. Medical history: He has been diagnosed with nephrolithiasis and gastritis a year ago. Negative family history. Blood biochemistry: Ca^{2+} level 2 mmol/l (N1.13–1.32 mmol/l), total calcemia 17.6 mg/dl (N 8.5–10), Phosphorus 2 mg/dl, Mg^{2+}1.5 mg/dl, Hct 35,3%, Hgb11.3 g/dl, WBC: 5900/mm^3, urea: 69 mg/dl, creatinine 1.6 mg/dl, sodium 144 mmol/l, potassium 3.7 mmmol/l, glucose 83 mg/dl, ALT 11U/l, AST 14U/l, GGT15U/l, LDH 140 U/l, Bilirubin Total 0.4 mg/dl, Chol 118, Tg 98, ferritinemia 89 mg/dl,TSH 1.49 ui/ml, Protein total 6.8 mg/dl. HGA resulted normal. Kidney ultrasonography: kidneys with calcifications of the pyramids, decreased cortico-medullary differentiation. Fundus oculi normal. Firstly we thought for chronic renal disease third stage in a subject with nephrocalcinosis. We performed PTH 745 ng/l (N15-65), 25 OH Vitamin D3 (16.3 ng/dl). We suspected a parathyroid gland disease, so we performed, Thyroid ultasonography: Right thyroid lobe normal, Left thyroid lobe with a well-restricted heterogeneous nodus, with internal cystic degenerations of 19×23 mm in the lower medial part. Isthmus normal. Thyroid shintiscan: with a hypofixant zone at the lower part of left thyroid lobe. Parathyroid scintigraphy resulted with parathyroid adenoma located at lower part of left thyroid lobe. Bone densitometry(DXA) showed in the forearm bones, high-risk osteoporosis with Tscore-5.4,osteopenia in femoral head and L4 lumbar vertebrae expressed osteoporosis,genetic testing was not done. He was treated with fluids i/v, diuretics, antihypertensives drugs. After diagnostic work-up,we concluded to PHPTcaused by parathyroid adenoma and the patient underwent surgical intervention with left hemithyroidectomy and left lower parathyroidectomy. Pathological examination: atypical parathyroid adenoma. After surgery he was treated with calcium orally and he was follow-up with PTH

level, calcium level and DXA.We think that his problem was resolved by surgery. He continues to be stable, under nephrologist and endocrinologist follow up.
Conclusion
PHPT is a rare situation in a young person. A nephrocalcinosis can be related to PHPT. Given the low frequency of atypical parathyroid adenoma,especially in young individuals, physician should always raise awareness of possible PHPT as cause of nephrocalcinosis and kidney injury, for early diagnosis and treatment. Nephrocalcinosis may be the presenting feature of atypical parathyroid adenoma,our case confirmes that.

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Cardiovascular Endocrinology and Lipid Metabolism

P261

Is there a relationship between mean platelet volume as a cardiac marker and serum calcium levels in patients with parathyroid disease

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Introduction and aims
Mean platelet volume (MPV) is a newly indicator of platelet activation which was associated with atherosclerosis. There are limited studies in the literature about MPV levels in patients with both hypoparathyroidism and hyperparathyroidism. This preliminary study, we aimed to investigate a relationship with MPV and serum PTH and calcium levels in patients with disorder of calcium metabolism.
Materials and methods
Fourty-nine hyperparathyroid patient (56.8±13.0 year), 13 hypoparathyroid patients (48.5±14.2 year) and 18 healthy subjects (45.2±14.2 year) were included in our study. All data associated with calcium metabolism including serum total calcium, phosphor, 25-OH vitamin D, parathyroid hormone levels were compared to study groups. All complete blood count, biochemical and hormonal analysis were performed by automatic analyzer.
Results
Serum total calcium levels were different between study groups (10.3±0.8 mg/dl in hyperparathyroid patient, 8.3±1.1 mg/dl in hypoparathyroid patients, and 9.3±0.4 mg/dl in control group, $P=0{,}0001$, respectively). There was no significant difference in MPV value (9.7±0.8 fl in hyperparathyroidism, 9.8±0.9 fl in hypoparathyroidism, 9.5±0.5 fl in control group, $P>0.05$, respectively]. In addition, there was not any correlation between MPV and all studied parameters of associate of calcium metabolism. Preliminary results was presented in this article, but we continue to the study.
Conclusions
Our findings do not support the existence of a relationship between MPV and calcium metabolism. However, preliminary results was presented in this article, we continue to the study.

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Clinical Case Reports Pituitary/Adrenal

P262

Hypercalcemia, hypercortisolism and multiple vertebral fractures in a 49-year-old man

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Introduction
The most frequent causes of hypercalcemia in the general population are primary hyperparathyroidism and malignancies. However, we must sometimes consider other causes, such as Cushing's syndrome.
Clinical case
A 49-year-old man who was being assessed for hypertrophic cardiomyopathy was referred to our Endocrinology Clinic in order to investigate the incidental finding of hypercalcemia (11.08 mg/dl) with high PTH (84.6 pg/ml), hypophosphatemia (1.84 mg/dl) and low 25-hydroxy vitamin D (11.9 ng/ml). He was a former smoker with history of hypertension, type 2 diabetes mellitus, dyslipidaemia and sensorimotor axonal polyneuropathy. He was unable to stand upraight and walked with a cane because of limb weakness and intense lumbar pain. He had lost 10 kg in the previous month, and complained of asthenia and constipation with haematochezia. Examination revealed BMI 29.07 kg/m^2, BP 173/99 mmHg, aortic systolic murmur, skin bruising, neck hump and proximal limb muscle atrophy. Amyloidosis and multiple myeloma were ruled out. Bone densitometry and lumbar CT showed severe osteopenia and multiple vertebral fractures. Neck ultrasound showed a lesion suggestive of parathyroid adenoma, but the parathyroid scan showed no evidence of hyperparathyroidism. Fasting plasma cortisol was 38.6 µg/dl, and 51 µg/dl after 1 mg overnight dexamethasone suppression test. The 24 h urinary free cortisol level was 718 µg/dl. He was admitted in our Endocrinology Department for Cushing's syndrome workup. The lab tests: ACTH 98.30 pg/ml, FSH 1.28 mUI/ml, LH 0.85 mUI/ml, free testosterone 0.76 mg/dl, FT4 0.62 ng/ml, TSH 0.58 ng/ml prolactine 12.1 ng/dl. A cranial MRI showed a pituitary tumor measuring 1.6×1.6×0.8 cm. The final diagnosis was Cushing's disease and hypogonadism due to a pituitary adenoma. An abdominal scan was performed to evaluate haematochezia and weight loss, and a mass of 1.5×6 cm was found in the rectum along with multiple lesions in the liver suggestive of haemangioma but needing further confirmation.
Conclusion
In this clinical case hypercalcemia was the key symptom which guided us to the final diagnosis of Cushing's disease. This is an unusual presentation, but the typical comorbidities (diabetes, central obesity, dyslipidaemia and hypertension) and complications (bone fractures) were present. With the presence of hyperparathyroidism, pituitary adenoma and a gastrointestinal mass, a MEN-1 syndrome must be considered. This case emphasizes the need for a comprehensive workup of the hypercalcemic patient.

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Severe hypercalcemia due to atypical parathyroid adenoma

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Introduction
Primary hyperparathyrodism is due to benign parathyroid adenomas in more than 90% and parathyroid cancer (PC) in less than 1% of cases. There are no definite clinical criteria differentiating PCs and adenomas. Another subtype, parathyroid neoplasm of uncertain potential is also referred as atypical parathyroid adenoma (APA) and share a few histopathologic features common to cancers.
Case
A 47 year old female patient was consulted due to hypercalcemia (total calcium 23.3 mg/dl) and admitted to endocrinology clinic. She was complaining of nausea, vomiting, vague abdominal and skeletal pain, fatigue, and muscle weaknees for 1 month. Her past medical history was nonsignificant. She denied urolithiasis and fracture due to osteoporosis. On physical examination oral mucosa was dry, and thyroid palpable on left side. We suspected PC or another malignancy related hypercalcemia due to severe hypercalcemia. Saline, furosemide, and zoledronate were infused along with subcutaneous calcitonin. Laboratory studies revealed high parathyroid hormone (PTH) (3134 pg/ml), hypercalciuria (381 mg/day), and vitamin D deficiency (8.2 ng/ml). *T* score and *Z* score of femur neck and lumbar spine were −3.5 on DEXA study. 4 days after admission calcium level was normalized. Impaired phosphorus, creatinine, and potassium levels improved with therapy. Neck ultrasound revealed a hypoechoic nodule 32.7×24.0 mm in size without suspicious lymph nodes. Tc-MIBI scan revealed increased uptake. A lobulated heterogenous mass 32×28 mm in size in close proximity to oesophagus was observed on contrast enhanced thorax-neck CT series. Invasion to neighbouring tissues and pathologic lymphadenopathies were absent. Histopathologic evaluation yielded an encapsulated parathyroid adenoma measuring 40×30×20 mm in size and equivocal areas of capsular invasion. Stains for PTH, Cyclin D1, and p53 were positive and negative for TTF-1 (−). Kİ67 was %15. Neither HRPT2 gene mutation analysis nor immunostain for parafibromin were available. After successful operation, PTH dropped to 82.6 pg/ml and a nadir of 19.4 pg/ml. While minimum calcium level was 7.8 mg/dl on 5th day of the operation, ALP reached 555 U/l at maximum. She was eucalcemic at the last time she was seen.
Conclusion
There is no single histologic feature pathognomonic of PC and APAs. APAs may present with severe hypercalcemia and very high levels of PTH similar to parathyroid cancers. The definition vascular invasion is also important. APAs must be kept in mind in differential diagnosis of primary hyperparathyroidism.

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P264

Functional hypoparathyroidism secondary to magnesium deficiency in long-term users of proton pump inhibitor: case report

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Introduction
Gastroesophageal reflux disease (GERD) is now widely prevalent around the world, with clear evidence of increasing prevalence in many developing countries. Treatment for most people with GERD includes lifestyle changes and medication. Proton pump inhibitors (PPIs) are a mainstay therapy for all gastric acid-related diseases. Long-term use of PPIs is associated with hypomagnesaemia, hypokalemia, hypocalcaemia, osteoporosis and bone fractures, renal disease, and other. Clinical concerns arise from a small but growing number of case reports presenting PPI-induced hypomagnesaemia as a consequence of long-term PPIs use.
Case report
We present the case of a 56-year-old patient with muscle cramps, violation of cardiac rhythm, lethargy and other caused by hypomagnesaemia (magnesium, 0.31 mmol/l), hypocalcaemia (calcium, 1.82 mmol/l), hypokalemia (kalium, 3.2 mmol/l) and hyperglycemia (6.7 mmol/l) with a low parathyroid hormone level (parathyroid hormone, 0.7 pg/ml). He had GERD and had been using a PPI (omeprazole 20-60 mg/day) since 2005. Physical examination revealed clinical signs of hypocalcaemia, hypomagnesaemia (Chvostek's and Trousseau's signs), hypokalemia. He had electrocardiogram abnormalities (prolonged QT interval, paroxysmal supraventricular tachycardia). After exclusion of possible causes, hypomagnesaemia secondary to PPI was diagnosed and omeprazole was stopping. Hypomagnesemia is often associated with hypokalemia (due to urinary potassium wasting) and hypocalcemia (due both to lower parathyroid hormone secretion and end-organ resistance to its effect). After only magnesium repletion all abnormalities resolved, his symptoms improved. It was shown association between hypomagnesemia and hypocalcemia, hypokalemia, hyperglycemia. A causal relation with PPI use was supported by the recurrence of hypomagnesaemia after re-challenge.
Conclusion
GERD patients using PPI should have their magnesium, kalium and calcium serum levels measured periodically, and non-specific symptoms such as asthenia, paresthesia or life-threatening manifestations (seizures, arrhythmias) should not be neglected.

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P265

Utility of ^{11}C-methionine PET/CT in preoperative localization of a parathyroid adenoma in a patient with primary hyperparathyroidism: a case report

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Introduction
Parathyroid adenoma is the most common cause of primary hyperparathyroidism. Effective preoperative imaging and localizing the parathyroid adenoma is a prerequisite for the surgical treatment. 99mTc-MIBI scintigraphy in combination with ultrasound of the neck are the imaging modalities of choice before parathyroidectomy. However, both have limitations in terms of their efficacy in localizing the adenomas; ^{11}C-Methionine or 18F-Fluorocholine PET/CT has been reported to have utility in such cases.
Case report
We present a case of a 55-year-old woman with a long-lasting history of recurrent nephrolithiasis, and osteopenia, who was diagnosed with primary hyperparathyroidism. Two 99mTc-MIBI SPECT/CT scans were performed (2/2015 and 09/2015), and neither identified the parathyroid adenoma. ^{11}C-Methionine PET/CT was then performed (04/2016), and revealed the parathyroid adenoma as a focal (7×9 mm in size) uptake of the tracer behind the lower part of the right thyroid lobe.
Conclusions
^{11}C-MET PET/CT has utility in preoperative localization of a parathyroid adenoma negative on 99mTc-MIBI scintigraphy in patients with primary hyperparathyroidism, and should be considered as a second-line imaging in such cases.

Keywords: primary hyperparathyroidism, ^{11}C-MET PET/CT, 99mTc-MIBI scintigraphy
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P266

Ulnar osteoclastoma as first manifestation in primary hyperparathyroidism: case report

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Background
Nowadays, primary hyperparathyroidism is usually diagnosed incidentally, in asymptomatic patients, while only around 15% of patients present the classical manifestations. Osteoclastoma, a benign bone lesion, is usually the late manifestation of hyperparathyroidism.
Objective
We present the case of a 52 years old female (non-menopausal) recently diagnosed with ulnar osteoclastoma, primary hyperparathyroidism and secondary osteoporosis.
Material and methods
The patient had a history of pathological fracture of right ulna secondary to osteoclastoma; she had undergone surgery removal of the tumor followed by bone grafting and screw fixation one year before being admitted to our hospital. At admission to our hospital, the patient had walking difficulties caused by the harvesting of fibular graft. Except for this, the physical exam was unremarkable. Laboratory findings revealed hypercalcemia (11.8 mg/dl), hypophosphatemia (2.2 mg/dl), low 25(OH)vitamin D level (6.45 ng/ml), high level of PTH (811.7 pg/ml) and elevated level of 24-h urinary calcium excretion (374 mg/24 h). Screening for multiple endocrine neoplasia type 1 and type 2A was negative. Neck ultrasonography revealed a hypoechoic mass (2.5/1 cm) suggestive for a lower right parathyroid adenoma. DXA of the lumbar spine, left hip and left radius showed low mineral bone density: L1–L3 T score = −3.8 S.D., Z score = −3.2 S.D., left hip (neck) T score = −3 S.D., Z score = −2.3 SD, distal left radius T score = −2.1 S.D. Z score = −1.9 S.D.. Abdominal ultrasonography showed bilateral renal microlithiasis.
Results
Clinical and paraclinical findings led to the diagnosis of primary hyperparathyroidism that eventually caused ulnar osteoclastoma and secondary osteoporosis. We recommended sestamibi parathyroid scintigraphy for adequate localization of the adenoma, followed by surgical removal. Based on the DXA score, we decided to initiate antiosteoporotic treatment with denosumab 60 mg 1 injection/6 months and supplementation with 1000 IU vitamin D3.
Conclusions
Although the classical hyperparathyroidism is not frequent nowadays, this diagnosis should be taken into consideration when dealing with osteolytic bone lesions such as osteoclastomas, so that proper treatment could be initiated. In the case we presented above, the late diagnosis of primary hyperparathyroidism led to multiple complications such as ulnar osteoclastoma with pathological fracture and secondary osteoporosis.

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P267

Lithium-associated Hyperparathyroidism in a Filipino woman presenting as recurrent ischemic stroke: a case report

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Background
Lithium salts have been widely known to induce thyroid dysfunction, however, parathyroid dysfunction due to lithium use is uncommonly encountered. Hypercalcemia is a relatively common consequence of lithium therapy presenting with nonspecific symptoms that may be overlooked. Although cerebral infarction may be an independent event from psychiatric disorders, it can also be a rare complication that must be recognized particularly in patients on lithium therapy.
Case
A 64-year old female diagnosed with bipolar disorder and maintained on Lithium for 25 years, noted to have multiple recurrent cerebral infarctions presenting as dizziness, headache and vomiting. She had a multinodular nontoxic goiter and osteoporosis. Work-up showed elevated ionized calcium and intact PTH, with evidence of bilateral renal parenchymal calcifications and the parathyroid scintigraphy revealed two Sestamibi-avid nodules.

Discussion
Hypercalcemia and hyperparathyroidism are common but often unrecognized consequences of lithium therapy. Lithium causes a shift in the inhibitory set point for PTH secretion to a higher serum calcium concentration and, although rare, complications include cerebral infarction due to hypercalcemia and should be watched out for in these patients. Single as well as multigland involvement may be seen in patients with LAH and preoperative localization studies should be done in patients with surgical indications. The low incidence of lithium-associated hyperparathyroidism limits acquisition of enough information for formulation of clinical guidelines for diagnosis and management, hence documentation and reporting of cases are important contribution for a larger pool of data.

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Looked like a goiter, proved to be a giant parathyroid adenoma

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Primary hyperparathyroidism is the third most common endocrine disorder, caused, in the majority of cases, by a single parathyroid adenoma and rarely by multigland adenoma or parathyroid carcinoma. Giant parathyroid adenomas, defined as larger than 3 g, represent an uncommon cause of primary hyperparathyroidism, with only a few cases described in the literature. We present the case of a 47 years old female who presented with a significant, unpainful, left cervical mass associated to light symptoms of fatigue, minor polyuria and hypercalcemia >3 mmol/l. Hormonal testing revealed very important elevation of parathyroid hormone, low phosphatemia and hypercalciuria, with preserved renal function. Ultrasound of the cervical region found a nodular, solid lesion, hyperechoic with hypoechoic areas and multiple microcysts measuring 7.6 cm of greatest diameter, in contact with the inferior pole of the left thyroid lobe. 99Tc sestamibi scan was positive for a voluminous inferior left-sided, hyperfunctioning parathyroid adenoma. CT scan confirmed the mass and described a right deviation of the trachea. Fine needle aspiration found cellularity compatible with parathyroid tissue. After controlling calcium levels, surgery was performed, consisting of removal of the mass as well as the left thyroid lobe attached to it. The parathyroid lesion measured 9×6, 3×3, 5 cm and weighted 80 g. Histological diagnosis was challenging because of relative capsule invasion and demanded second opinion to finally conclude in favor of a benign adenoma. Early postoperative calcium and active vitamin D supplementation was necessary to keep normal calcium levels. Parathyroid adenomas weighing more than 70 g are extremely rare. Our patient presented the second biggest giant parathyroid adenoma described to date. Surpisingly, despite its dimensions, this giant parathyroid adenoma did not cause severe hypercalcemic or local pressure symptoms. Differential diagnosis with a parathyroid carcinoma represented the greatest difficulty prior to surgery, as well as histologically due to several overlapping characteristics.

Keywords: primary hyperparathyroidism, giant parathyroid adenoma, cervical mass, hypercalcemia, parathyroid carcinoma

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P269

Concomitant primary hyperparathyroidism with papillary thyroid carcinoma: The role of dual-phase ^{99m}Tc-MIBI parathyroid imaging: case report

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Introduction
Although concomitant primary hyperparathyroidism (PHPT) and papillary thyroid carcinoma (PTC) has been repeatedly reported in medical literature with an incidence of 2.3–4.3%, no causal relationship has been elucidated. In most cases, diagnosis of PTC is mostly incidentally, while PHPT is usually the primary pathology. Recent literature supports the possible role of dual-phase ^{99m}Tc-MIBI parathyroid imaging in detecting PTC in patients with PHPT.
Case report
We present the case of a 47-year-old woman, recently diagnosed with nodular goiter and severe osteoporosis. Work up of the patient revealed increased levels of serum calcium and low level of phosphorus, high level of intact parathormone and hypercalciuria, consistent with primary hyperparathyroidism. Neck ultrasound identified a hypoechoic thyroid nodule, with macrocalcifications and intranodular vascularisation. The $^{99m}TcO_4$ -thyroid scan described no uptake of radiopharmaceutical in the left upper thyroid lobe. The ^{99m}Tc-MIBI scan revealed an increased uptake in the left lower thyroid lobe, and also in the left upper thyroid lobe. A diagnosis of PHPT and nodular goiter was established. The patient underwent parathyroidectomy and left thyroid lobectomy. After surgery, PHPT was biochemically cured. Histopathological examination revealed parathyroid adenoma in the left lower parathyroid gland, and papillary carcinoma in the suspect thyroid nodule. The completion of thyroidectomy was performed after 3 months. Patient underwent radioiodine ablation therapy, actually being on suppressive T4 treatment.
Conclusions
Even concurrent parathyroid adenoma and papillary thyroid carcinoma is rare, they may coexist. Prior to undergoing parathyroid surgery for PHPT, it's indicated to carefully screen for thyroid disease, to avoid a second surgery. Dual-phase 99mTc-MIBI parathyroid imaging may be useful in detecting both parathyroid adenoma and papillary thyroid carcinoma.

Keywords: Primary hyperparathyroidism, papillary thyroid carcinoma, 99mTc-MIBI parathyroid imaging

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Multiple brown tumors inprimary hyperparathyroidismcaused by an adenoma mimicking metastatic bone disease with false positive results on computed tomography

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Introduction
Brown tumors are bone lesions that arise due to osteoclastic activity and may mimic a true neoplasm. We encountered an unusual case of hyperparathyroidism with multiple brown tumors that mimicked metastatic bone tumor due to false positive results on computed tomography (CT).
Case
60 year old gentleman presented to the medicine out patient department with complains of fever, cough and right chest pain. Due to severe chest infection he was admitted, and CT scan was done. CT scan showed multiple lytic lesion in bilateral ribs with some areas of cortical breach suggestive of metastasis/multiple myeloma/enchondroma along with multiple calcifications in bilateral kidneys. With all the differentials in mind patient was evaluated. M Band was negative with high corrected calcium. Intact PTH was very high (3050 pg/ml: normal 9–55 pg/ml). On neck examination 3×2 cm nodule was palpable.With the report of high PTH and high calcium diagnosis of primary hyperparathyroidism was made with the doubt whether it's a palpable parathyroid carcinoma with bone metstasis. USG neck revealed hypoechoic lesion posterior to left inferior lobe of thyroid of 3.6 cm. As no MIBI scan was available in the vicinity, we went ahead with exploration. 4×3 cm lesion was found adherent to thyroid. Therefore enbloc excision was done with hemithyroidectomy. After resection, the patient's serum levels of calcium, alkaline phosphatase, and intact-PTH normalized Post-operatively patient developed clinical and biochemical hypocalcemia and managed with calcium infusion. Histopatholgy turned out to be parathyroid adenoma.
Conclusion
Palpable parathyroid tumor, advanced skeletal and very high serum calcium with parathyroid hormone levels are considered strong predictors of parathyroid carcinoma. Most of these features are common in Indian primary hyperparathyroidism (PHPT) patients although only few have Parathyroid carcinoma [1].
Reference
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Regression of multipl brown tumors after surgical removal of mediastinal ectopic parathyroid adenoma

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Introduction
Parathyroid adenoma is the most common cause of primer hyperparathyroidism (PHPT). Mediastinal ectopic parathyroid adenomas constitute about 1–3% of the cases. Brown tumors ocur in less than 2% of the patients with PHPT. Moreover, those skeletal manifestations are even rarely demonstrated with maxillofacial bones involvement.
Case presentaton
Here we report a 36-years-old woman presented with approximately 30×26 mm mass growth in her mandible. She had been suspected for malignancy because of detected hypercalcemia and multipl lytic bone lesions. However, the biopsy of femur has been reported with no evidence of malignancy. Our laboratory findings revealed PTH dependent hypercalcemia (Calcium = 12.76 mg/dl (8.6–10.2), PTH = 1373 pg/ml (15–65), P = 1.8 (2.6–4.5), Mg = 1.93 mg/dl (1.6–2.6), creatinin = 0.73 mg/dl (0–0.95), ALP = 401 U/L (35–105), 24 h urinaryCa = 450 mg/24 h (100–300)). In bone scintigraphy, multipl foci of technetium-99 m uptake in calvarium, mandible, sternoclavicular joint, bilateral humerus, femur, sacroiliac joint, right iliac crest, costa and vertebra were detected. Maxillofacial CT scan identified multiple expansile lesions from 10×9 to 30×26 mm in frontal bone, hard palate, maxillary sinüs and mandible. Cervical sonography was unremarkable. Tc-99-m-MIBI scintigraphy revealed a 20 mm parathyroid lesion in the anterior mediastinum at subcarinal level. After intravenous hydration, loop diuretic, bisphosphonate and cinacalcet treatment, a thoracoscopic surgery was performed. The histopathology of the tissue was consisted with a parathyroid adenoma. Hungry bone syndrome occured following surgery and was treated with oral calcium and calcitriol for about 10 months. Over a year later, she has normal serum calcium and PTH levels. Control CT scan revealed a remarkable regression in Brown tumors and some of them did not even detected.
Conclusion
Brown tumors may mimic cancer metastasis therefore can be misdiagnosed. Physicians should always consider PHPT in the differential diagnosis. The most important way to distinguish these skeletal manifestations of PHPT from malignancy is by biochemical analysis with serum calcium and PTH levels. For localisation of PHPT, ectopic locations should also be evaluated if neck imagination reveals no lesion.

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Multiple hormone resistance in a patient with follicular thyroid carcinoma and papillary microcarcinoma

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Pseudohypoparathyroidism and related hormone resistance disorders have very heterogeneous clinical course and might be recognized only in the adulthood, particularly with the development of hypocalcemia. We present a 41 years old male patient who underwent a neurological investigation because of progressive muscle weakness and elevated creatinine kinase. Very low serum calcium (1.46 mmol/l) with hyperphosphatemia, low magnesium and high normal PTH were measured. The patient also had slightly higher LH and high FSH with low normal free testosterone, 46 XY karyotype and testes of normal volume. Lumbar bone mineral density was increased. TSH was just over the reference range and thyroxine was normal. On the neck ultrasound 3 cm large suspicious nodule was found in the left thyroid lobe. FNA suggested follicular tumour and left thyroid lobectomy discovered follicular carcinoma with capsular invasion and papillary microcarcinoma. The patient was reoperated for right thyroid lobectomy and radioiodine ablation therapy was further performed. Postoperative PTH was low due to incidental parathyroidectomy. Malignant thyroid disease indicated the need for TSH suppression, but his TSH was persistently elevated despite increasing L-T4 dose up to 250 µg. Free T4 levels also rose and patient had thyrotoxic symptoms. High SHBG reflected tissue thyrotoxicosis. The combination of L-T4 and L-T3 therapy finally succeeded to decrease TSH to the middle of the normal reference range and SHBG was used as an additional marker for its optimization. We presumed that this patient has multiple hormone resistance associated with deficient G-protein α subunit signalling, involving at least PTH and gonadotropins. Low magnesium levels might have contributed to the breakdown of PTH and calcium balance that triggered hypocalcemia. Gonadotropin resistance did not interfere with male phenotype development and some physical features might appear as mild Albright's hereditary osteodystrophy. TSH resistance might also be found in such patients, but TSH is expected to fall promptly with L-T4 therapy. However, our patient showed inadequate responsiveness to L-T4 therapy suggesting a probable defect in thyroid hormone transport or deiodination. This was partially circumvented with L-T3 treatment, but uncertainties remain whether unsuppressed TSH might have negative impact on the risk for thyroid carcinoma recurrence. In this case we were faced with unexpected challenges of replacement therapy that could not be directly related with the primary disorder. Further genetic evaluation might contribute to our clinical assessment or even point to the common pathogenesis of this patient's clinical presentation.

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Hypercalcemia not mediated by PTH: a case report

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Introduction
Hypercalcemia is a frequent hydroelectrolytic disorder, and primary hyperparathyroidism is the most common cause in oupatients. It is important to make an early diagnosis and adequate treatment in order to avoid possible complications such as nephrolithiasis, osteoporosis or the deterioration of glomerular filtration rate.
Clinical case
A 63-year-old female patient referred for hypercalcemia. Past medical history included stage IV chronic renal failure (with more marked deterioration of glomerular filtration in the last year) and recurrent bronchitis. She had polydipsia, polyuria, asthenia and 10 kg weight loss in the last year. Physical exam was normal except for mobile, soft bilateral supraclavicular, axillary and inguinal lymphadenopathies. Laboratory findings were as follow: Creatinine: 2.32 mg/dl (0.51–0.95), Corrected calcium:14.19 mg/dl (8.1–10.5), Phosphorus: 3.5 mg/dl (2.5–4.5), Angiotensin converting enzyme: 242 U/L (8.0–52), Parathormone related protein: <1.10 pmol /L (0.00–1.50); 1,25 hydroxyvitamin D: 99 pg/mL (16-56), intact PTH: 7.8 pg/mL (10.0–65.0), 25 hydroxyvitamin D: 18.3 ng/mL (Deficit: <20), Calcium/creatinine: 0.652, B2microglobulin: 11.06 mcg/ml (0.80–2.34), Leukocytes: 7750 10E3/µl (4.50–11.00), Erythrocyte sedimentation rate: 30 mm (1–20). No Monoclonal Component was evidenced. Bacilloscopy and mycobacterial culture: Negative, QuantiFERON-TB: Negative. Thorax radiography: Bilateral hilar adenopathies, without clear interstitial pattern. High resolution tomography: Supraclavicular, mediastinal, hilar, axillary, retrocrural, abdominopelvic, iliac and inguinal adenopathies; bilateral subpleural nodular lesions, focal splenic lesion of 0.8×0.70 mm. Biopsy of supraclavicular nodes showed non-necrotizing granulomas compatible with Sarcoidosis. Improvement of calcemia and renal function was obtained with intravenous hydration. After confirming the diagnosis of sarcoidosis, treatment with corticosteroids and hydroxychloroquine was initiated (current: corrected calcium 10.78 mg/dl; Cr 1.47 mg/dl)
Conclusion
Sarcoidosis is a rare cause of hypercalcemia, wich occurs as a result of the overexpression of the enzyme 1α-hydroxylase in the macrophages of granulomas (with the consequent increase of 1, 25-OH-vitamin D). It is essential to considered it in the differential diagnosis of non-PTH-dependent hypercalcemia.

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Papillary thyroid cancer and primary hyperparathyroidism – a rare coincidence: case report

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Introduction
Although co-association between thyroid disease and parathyroid disease is rare, co-existence between parathyroid adenomas (HPPs) and papillary thyroid carcinomas (PTC) is rare. Perhaps this can be explained by the different embryological origins of the thyroids cells with the parathyroid cells.
Objectives
To report a case with parathyroid adenoma and multifocal papillary thyroid carcinoma.
Case presentation
A 62-year-old woman presented in the Endocrinology service due to a hypercalcemia 12.1 mg/dl (normal, 9.0–10.6 mg/dL), detected during routine biochemical evaluation for recidive kidney stone. High PTH value 280 pg/ml (normal range 10–69 pg/ml) confirmed primary hyperparathyroidism The neck ultrasound showed a potential parathyroid adenoma (nodule size 12×8 mm right lobe) as well as a nodule on the left lobe 24×10 mm. ^{99m}Tc-sestamibi parathyroid scintigraphy indicated an area with increased uptake at the aria of the nodule presented at ultrasonography. Because of the nodular aspect of the contralateral lobe: total thyroidectomy was performed and the histological examination the diagnosis of parathyroid adenoma and coincidence of invasive multifocal papillary thyroid carcinoma in the left thyroid lobe.). Hyperparathyroidism was cured with normal PTH and for the invasive PTC she received radioiodine therapy and now she is on suppressive LT4 treatment.
Conclusion
Careful evaluation of thyroid gland is advocated in all patients of primary hyperparathyroidism in order to prevent subsequent operations.

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Endocrine Disruptors

P275

Role of Pro-inflammatory cytokines in Primary Hyperparathyroidism: A Prospective Study

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Introduction
Primary Hyperparathyroidism (PHPT) is a frequent endocrine disease which requires surgical excision for definitive cure. Apart from genetic role in its pathogenesis, there are conflicting reports about role of immunomodulation in literature. In this context, we set out study the role of Pro- inflammatory cytokines in PHPT in South Indian population.
Material and methods
This prospective case-control study was conducted on surgically managed PHPT patients. Institutional ethical committee approval was obtained. Diagnosis of PHPT was based on biochemical confirmation, imaging, MIBI scanning and later confirmed by histopathology. Exclusion criteria were subjects with any systemic or chronic inflammatory disease or any medication which interferes with the normal function of the hypothalamic-pituitary-gonadal axis. Serum samples were collected from 21 PHPT subjects and 20 age matched healthy controls. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF-α) and high sensitive C reactive protein (hsCRP), leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.
Results
The mean hSCRP level in PHPT and controls were 12.3 ± 3.6 mg/mL and 6.7 ± 1.3 mg/mL respectively. The mean TNF-α level and IL-6 level and Leptin levels were 189 ± 22.5 pg/mL, 16.4 ± 2.9 pg/mL and 3.1 ± 1.4 ng/mL respectively. Serum leptin level in controls was 3.7 ± 2.1 ng/mL. There was statistically significant difference of hsCRP and IL-6 level (P value < 0.05). There was no statistically significant difference of TNF-α and leptin between cases and controls (P value > 0.05).
Conclusions
This study shows raised titers of pro-inflammatory markers – IL-6 and hsCRP, while TNF-α and Leptin levels had neutral association with PHPT. But, the exact immuno-modulatory role and pathogenetic mechanism needs more investigational research.
Keywords: Hyperparathyroidism, Tumour necrosis factor, Interleukin-6, Hypercalcemia, Auto-immunity, Leptin

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Endocrine Nursing

P276

Prevalence of kidney stones and osteoporosis in patients with primary hyperparathyroidism

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Aim
The main aim of this study was to evaluate the prevalence of kidney stones and osteoporosis in a cohort of patients with a confirmed diagnosis of primary hyperparathyroidism (PHPT).
Study design
This retrospective study reviewed the clinical records of patients with a confirmed diagnosis of PHPT in a single tertiary referral centre for metabolic bone disease over a period of 6 years (January 2010 – December 2015).
Patients
There were a total of 258 patients included in the study. 206 women (173 post-menopausal and 33 pre-menopausal) and 52 men with mean age of $63.5+14.84$ years.
Method
The clinical records of 258 patients were scrutinised to determine the prevalence of kidney stones (as identified by abdominal ultrasound or X-ray or computed tomography scan) and osteoporosis (defined as bone mineral density T-score of <-2.5 measured by dual-energy X-ray absorptiometry [DXA]). The prevalence of kidney stones and osteoporosis were compared between the symptomatic and asymptomatic PHPT patients.
Results
The prevalence of kidney stones in those who had undergone renal imaging was 13.86% (28 out of 202). There was no difference in the prevalence of kidney stones between the symptomatic and asymptomatic patients (15.45% versus 11.96%, $P=0.5428$). The prevalence of osteoporosis was found to be 43.62% (from 188 patients who had bone DXA scan). There was also no difference in the prevalence of osteoporosis between the symptomatic and asymptomatic patients (43.43% versus 43.82%, $P=1.0000$). Although only 27.13% of patients (70 out of 258) had urinary calcium excretion screening completed, symptomatic patients were found to have higher levels of urinary calcium compared with the asymptomatic patients (7.8 mmol/24 hours versus 4.4 mmol/24 hours, $P=0.0089$).
Conclusion
Kidney stones and osteoporosis are common in both symptomatic and asymptomatic PHPT patients. The results from this study provide further evidence of the need for a more rigorous and consistent evaluation of the kidneys and skeleton of patients diagnosed with PHPT in order to identify and manage these well- known end-organ complications appropriately.

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Endocrine Tumours and Neoplasia

P277

Somatostatin receptors 1 and 5 are novel markers of parathyroid tumor aggressiveness

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Background
Parathyroid carcinoma (PC) is a rare cause of primary hyperparathyroidism (PHPT). Distinguishing PC from other tumours underlying PHPT can be difficult and sometimes malignant diagnosis can be made only after recurrence of the disease. Atypical parathyroid adenomas (APA) have similar histological features as PC but lack signs of invasive growth. The expression of somatostatin receptors (SSTR) 1–5 in parathyroid tumours, commonly expressed in other neuroendocrine tumors, is currently not known.
Aim
To examine immunohistochemical expression of SSTRs 1–5 in parathyroid tumours: parathyroid adenomas (PA), APAs and PCs.
Methods
Nationwide cohort of PC ($n=32$), age- and gender-matched PA ($n=72$) and APA ($n=28$) were used. TMA blocks were stained with antibodies for SSTR subtypes 1–5 and intensity (0–3) of cytoplasmic, nuclear and membrane expression was

scored. Correlations of SSTRs with parafibromin, Ki-67, fibrous septae and biochemical and clinical characteristics were also analysed.
Results
Membrane expression was negligible for all receptor subtypes. Expression of **SSTR 2-3** was negative. Nuclear **SSTR1**, nuclear and cytoplasmic **SSTR4** and nuclear **SSTR5** expression increased- and cytoplasmic SSTR5 decreased with tumour aggressiveness:

Receptors with statistical significance and their relative expression in the tumor groups

	PA	APA	PC	*p*-value
Nuclear **SSTR1**	1.5%	15%	41%	<0.001
Cytoplasmic **SSTR4**	29%	40%	56%	0.027
Nuclear **SSTR4**	31%	51%	62%	0.008
Nuclear **SSTR5**	15%	51%	69%	<0.001
Cytoplasmic **SSTR5**	85%	78%	56%	0.02

Expression of nuclear SSTR5 was related to decreased parafibromin expression ($P=0.002$). Serum calcium and parathyroid hormone concentrations correlated with expression of nuclear SSTR1 ($P<0.001$), inversely with nuclear SSTR5 ($P<0.001$) and positively with cytoplasmic SSTR5 ($P=0.045$). Tumor size, fibrous septae and Ki-67 were related to expression of nuclear SSTR1 ($P=0.029$, $P<0.001$, $P=0.005$) and SSTR5 ($P=0.023$, $P<0.001$, $P<0.001$)
Conclusion
SSTR1 and SSTR5 expression may have a role in parathyroid tumour pathogenesis.
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Vitamin D and cancer of the prostate
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Introduction
Vitamin D deficiency has been found to be associated with multiple chronic diseases, including diabetes mellitus type 1 and 2, rheumatoid arthritis and other autoimmune diseases. However, the relationship between vitamin D and cancer remains controversial. Vitamin D deficiency is widely prevalent in the general population. In accordance, vitamin D deficiency was found to be prevalent in Scotland. In a study performed in Scotland vitamin D deficiency was observed, however, no relationship with specific cancers was found. Additionally, relationship between vitamin D receptor mutations and cancer of the prostate has been observed.
Aim
The aim was to estimate the relationship between vitamin D and cancer of the prostate.
Methods
In a group of 31 patients suffering from prostate cancer $25(OH)D_3$ levels, PTH levels and calcium levels were measured. Observations were also performed in 31 patients, male, in the same age group serving as controls.
Results
Vitamin D, $25(OH)D_3$ levels, were found to be 25.32 ± 1.9 ng/ml and 20.21 ± 2.37 ng/ml in the group of prostate cancer patients and the control group, respectively, ($P<0.001$).
Conclusions
The relationship between vitamin D and cancer remains controversial. A relationship has been observed between mutations of the vitamin D receptor and cancer of the prostate. However, the relationship between vitamin D deficiency and cancer is controversial. In the present study higher vitamin D levels were observed in prostate cancer patients as compared to a control group of men within the same age group. Therefore, when administering vitamin supplementation as well as vitamin D treatment for osteoporosis or osteomalacia caution should be exercised in order to keep vitamin D levels within the normal range. It should also be noted, that $25(OH)D_3$ exerts its effects by binding to its receptor within the core of the cell, thereby exerting powerful, important and as yet unknown effects in the human organism.
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P279

Feasibility and efficacy in ultrasound guided percutaneous microwave ablation of primary hyperparathyrodism with parathyroid nodules
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Purpose
To investigate the feasibility and efficacy of US-guided microwave ablation on primary hyperparathyrodism patients who were excluded from surgical treatment.
Materials and methods
From May 2014 to December 2017, 30 parathyroid nodules of 25 patients underwent percutaneous ultrasound-guided MWA in our department. Contrast enhanced ultrasonography, ^{99}Tmc-MIBI test, laboratory data and clinical symptoms were evaluated before therapy; 2 hours, 1, 3 days, 1 week and 1, 3, 6 and 12 months after treatment, and every 6-12 months thereafter.
Results
Twenty-two (88%) patients underwent successful ablation among total 25 patients, with 4 patients who underwent ablation of 2 nodules. Minor complications in 3 patients (12%) occurred, including transient fever and voice change.
Conclusions
MWA of hyperplastic parathyroid glands for treating primary HPT proved feasible and effective, while showing meaningful reduction in iPTH, calcium and phosphorus level, minor complications and satisfying clinical outcomes.
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Female Reproduction

P280

Association between age at onset of menopause and fracture risk: a systematic review and meta-analysis
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Introduction
Early menopause (defined as age of menopause <45 years) and premature ovarian failure (defined as age of menopause <40 years) are associated with accelerated bone loss and increased risk of osteoporosis in later life. However, their association with increased fracture risk has not been established, with studies yielding conflicting results. The aim of this study was to systematically review and meta-analyze studies evaluating the effect of age at onset of menopause on fracture risk.
Methods
Search was conducted in three databases (PubMed, Central, Embase). Eligible for the review were studies that have reported fractures (total, vertebral, non-vertebral, hip) in women with premature ovarian failure or early menopause versus women with natural menopause. Data were expressed as odds ratio (OR) with 95% confidence intervals (CI) and combined by the Dersimonian/Laird method. The I^2 index was employed to indicate heterogeneity; publication bias was inspected by Funnel plots and tested by the Egger's test. Meta-analysis was performed using RStudio (Version 1.0.414, RStudio, Inc.) and the programming language R (version 3.4.3, 2017, The R Foundation for Statistical Computing).
Result
Twelve (four case-control and eight cohort) studies, including a total of 39,510 postmenopausal women (9,668 of which with fractures), were eligible for qualitative and quantitative analysis. Women with premature ovarian failure (age $<$ 40 years) had similar probability of experience a fracture (OR: 1.24, 95% CI: 0.77–1.99, I^2: 58%, 5 studies) compared to women with age of menopause $>$ 40 years. Women with early menopause (age $<$ 45 years) had similar probability of experience a fracture (OR: 1.43, 95% CI: 0.87–2.36, I^2: 94%, 9 studies) compared to women with age of menopause $>$ 45 years.
Conclusions
There is no evidence that women with premature ovarian failure or early menopause experience higher bone fracture risk in later life compared to women with natural menopause. More prospective cohort studies with adequate sample sizes and superior methodological characteristics are needed in order to estimate the effect of early age of menopause on bone fractures.
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Poster Presentations: Diabetes, Obesity and Metabolism

Adrenal Cortex (to include Cushing's)

P281

Hypoglycemia in non-diabetic patients: clinical features and causes

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Introduction
Hypoglycemia in non-diabetic patients is a rare condition. Because of the non-specificity of its symptoms and the multiplicity of its causes, hypoglycemia represents often a diagnostic challenge for general practitioners. The aim of our study was to assess the clinical features of hypoglycemia and to determine its causes in non-diabetic patients.
Methods
We conducted a retrospective analysis in 49 non-diabetic patients who were admitted to our endocrinology department between 2012 and 2017 with a clinical suspicion of hypoglycemia. The diagnosis of hypoglycemia was established using Whipple's triad. In patients with confirmed hypoglycemia, clinical and paraclinical features were analyzed.
Results
Among the 49 participants, Whipple's triad was documented in only 40 patients. In the other patients, symptoms were secondary to cardiac arrhythmia, anxiety attack, hysteria and dizziness. The mean age of patients with confirmed hypoglycemia was 43 ± 19.57 years [14–80 years] and the sex-ratio (F/M) was 2.14. Thirty nine percent of our patients were unemployed and 65% of patients have a diabetic family's member. Hypoglycemia was severe in 51% of cases. Neurogenic symptoms were present in 97% of cases (sweating, palpitations and shakiness in 90%, 73% and 61% of cases, respectively). Neuroglycopenic signs were reported in 70% of cases: seizure and coma were found in 17% and 36% of cases, respectively.The mean concomitant blood glucose concentration was 0.37 ± 0.1g/l. Etiological investigations revealed reactive hypoglycemia in 21% of cases and organic hypoglycemia in 79% of cases. Adrenal insufficiency was diagnosed in 29% of cases, factitious hypoglycemia in 24% of cases, drug induced hypoglycemia in 15%, paraneoplastic hypoglycemia secondary to gastrointestinal stromal tumor was diagnosed in one case. In three cases, the cause of hypoglycemia was unknown.
Conclusion
Although autonomic and neuroglycopenic symptoms are highly suggestive of hypoglycemia, the diagnosis of hypoglycemia should be established only in the presence of Whipple's triad.Then, appropriate evaluation should be conducted in order to set up the underlying cause.

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Bone & Osteoporosis

P282

First report of Gaucher disease in Montenegro: Genotype/phenotype correlations

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Background
Gaucher disease (GD) is the most common lysosomal storage disorder. The defect is deficiency of lysosomal glucocerebrosidase (GBA), due to biallelic mutations in GBA gene, characterized by the deposition of GBA in cells of the macrophage-monocyte system.
Objective
To report clinical phenotypes of GD and correlate with GBA gene mutations, and to identify GBA gene mutation in patients diagnosed with GD in Montenegro.
Methods
Demographic and clinical phenotype was recorded for each patient in the study. The diagnosis was confirmed with low leucocyte acid beta glucosidase activity. GBA gene sequencing was performed after long range PCR for selective amplification of GBA active gene and analysis of the entire coding region.
Results
We report five patients (four male, one female) of type 1 GD. The age at diagnosis ranged from 7 to 40 years. Patients experienced delays of 1–12 years in diagnosis after onset of symptoms. Most common mode of presentation was variable degree of splenomegaly and thrombocytopenia; other symptoms included bone pain, hepatomegaly, abdominal pain and fatigue. Osteopenia was present in majority of the patients: 4/5. All patients had asymptomatic Erlenmeyer flask deformity of the distal femur. In one patient hepatitis B was diagnosed, one had Parkinsonism, and one low pulmonary diffusion capacity for carbon monoxide. On enzyme replacement therapy (ERT) the hematological and visceral parameters showed significant improvement, and no significant progression in bone mineral density was noticed. GBA gene sequencing revealed homozygosity for N370S mutation in one patient. Genotypes of other patients were N370S/55bp deletion, N370S/D409H (in two patients), and H255Q/N370S (one patient).
Conclusion
This is the first report of GD from Montenegro. N370S was the most common mutation occurred in all five patients, one patient was homozygous and others compound heterozygous. The phenotypes of GD1 encountered in Montenegro were severe but all responded well to ERT.

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Hip axis length in women with type 1 diabetes mellitus

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Objective
In the early manifestation of type 1 diabetes (T1D) the process of bone mineralization is disrupted and the peak of bone mass is initially lower than in healthy individuals. In addition to low mineralization T1D may be a risk factor for a smaller bone size including the hip axis length (HAL). The aim of this study is to assess the HAL in women with T1D.
Materials and methods
We examined 68 T1D women, age: 31(25–37.6)yrs., duration of diabetes: 11(7–17)yrs., HbA1c: 8.5(6.9–10.4)%, BMI: 23.4(22.3–25.8 kg/m^2). The control group consisted of 53 healthy age- and BMI-matched females. Bone mineral density (BMD) was measured with dual X-ray absorptiometry. Hip axis length (HAL) was determined using the Advanced Hip Analysis program.
Results
BMD (Z-score) of the femoral neck in the group T1D women was significantly lower (T1D: -0.5 ($(-1.1)-0.2$) vs. controls: 0.1 ($(-0.6)-0.7$), $P=0.006$ respectively) compared to control group. Previous low-energy fractures occurred more frequently in female with T1D (T1D: $n=10$ (14.7%) vs. controls: $n=2$ (3.9%), $F=0.033$, $P=0.042$ respectively). In women with T1D HAL was statistically shorter than in the control group (T1D: 104.8(100–109.8) vs. controls: 107.3(103.8–110.1), $P=0.018$ right femur; T1D: 106(100.2–110.2) vs. controls: 107.5(105.2–110.8), $P=0.035$ left femur respectively).
Conclusions
In women with T1D HAL was statistically shorter than in the control group. The results of our own research potentially indicate the structural changes of the hip geometry in women with T1D.

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Vertebral fractures in patients with type 2 diabetes mellitus

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The aim of study
Is to assess the frequency of occurrence of vertebral fractures (VFx) and their relationship with hip geometric parameters in type 2 diabetes mellitus (T2DM) postmenopausal women.
Materials and methods
We examined 94 T2DM women, age: 59.6(55.1–63.2)yrs., duration of DM: 7(4.5–11)yrs., duration of menopause 8.5(4–13)yrs., HbA1c:7.3(6.6–9.8)%). The comparison group consisted of 89 women without DM (age:58.3 (52.8–61.2)yrs., duration of menopause 8(3–11)yrs.). Bone mineral density (BMD) at lumbar spine and femoral neck and VFx were measured with dual X-ray absorptiometry. Geometric parameters were determined using Advanced Hip Analysis program. ISI-impact strength index was calculated using the formula of Karlamangla.
Results
It has been established that the BMD (T-score) of the lumbar spine (T2DM: $-1((-1.9)-0.1)$ vs. comparison gr.: $-0.8((-1.8)-0.1)$, $P=0.815$, respectively) and of the femoral neck (T2DM: $-0.7((-1.3)-0.2)$ vs. comparison gr.: $-0.7((-1.3)-0.1)$), $P=0.730$, respectively) in patients with T2DM is comparable with the comparison group, while the BMD of the proximal femur is higher in women with T2DM (T2DM: $0.3((-0.7)-1.4)$ vs. comparison gr.: $-0.1((-0.9)-0.7)$ $P=0.037$, respectively). VFx occur statistically significantly more often in patients with T2DM (T2DM:19.15%, $n=18$ vs. comparison gr.:7.87%, $n=7$, $X^2=4.935$, $P=0.026$). In patients with type 2 diabetes considering the OR and 95% of CI the high risk of VFx of 1, 2, and 3 degrees has been found in comparison with the women without DM (OR = 2.77, 95% CI = 1.098–7.012). T2D females with VFx had lower ISI (T2D with VFx: 0.22 (0.20–0.27) vs. T2D without VFx 0.25(0.23–0.28), $P=0.035$, respectively) and larger femoral neck diameter (T1D with VFx: 34.6(33.4–36) vs. T1D without VFx 32.9(31.5–34.8) $P=0.020$, respectively) compared with T1D females without VFx.
Conclusions
VFx statistically occur significantly more often in women with T2DM regardless of BMD. The obtained results testify to the lower ISI, larger femoral neck diameter in group T2DM with the presence of VFx.

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Vertebral fractures in women with type 1 diabetes mellitus

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Research object
Since type 1 diabetic (T1D) patients are at higher fracture risk in comparison to general population the aim of study was to assess, whether femur geometric parameters are connected with Fx in T1D females.
Materials and methods
We examined 68 T1D 31 yrs. old (25–37.6) females with disease duration of 11 (7–17) yrs. and the average HbA1c equal to 8.5 (6.9–10.4) %. The control group consisted of 53 healthy age- and BMI-matched females. Bone mineral density (BMD) and VFx were measured with dual X-ray absorptiometry. Geometric parameters were determined using Advanced Hip Analysis program.
Results
T1D females had lower BMD at femoral neck (T1D: Z-score $-0.5((-1.1)-0.2)$ vs controls: Z-score 0.1 $((-0.6)-0.7)$, $P=0.006$, respectively), higher frequency of fragility Fx (T1D: $n=10$ vs controls: $n=2$, $P=0.042$, respectively), VFx (T1D: $n=12$ vs controls: $n=1$, $P<0.01$, respectively) compared to controls. Differences in the hip geometric parameter of CSA in women did not reach a statistically significant difference, however, there was a tendency to decrease this parameter in the group of T1D women. Age, diabetes duration, age of diabetes manifestation, and the prevalence of chronic complications were not different between type 1 diabetics with and without VFx. When comparing patients with VFx and without it it was found that in patients with type 1 diabetes with a VFx the BMD (Z-score) is lower both at spine $(-1.7((-2.3)-(-1.0))$ vs $-0.3((-1.1)-0.5)$, $P<0.001$, respectively) and at femoral neck $(-1.4\pm1.1$ vs -0.5 ± 1.05, $P=0.002$, respectively) and the daily insulin dose per kg is higher (0.89(0.76–1.25) vs. 0.69(0.54–0.9), $P=0{,}010$ respectively). T1D females with VFx had lower CSMI (cross-sectional moment of inertia) (T1D with VFx: 7836 (6533–10377) vs. T1D without VFx 10140(8770–12522), $P=0.035$, respectively) and CSA (cross-sectional area) (T1D with VFx: 122(104–137) vs. T1D without VFx 144(129–165) $P=0.006$, respectively) compared with T1D females without VFx. In the logit regression analysis VFx were associated with BMD spine, CSA and daily insulin dose.
Conclusions
Type 1 diabetic women have low BMD, higher prevalence of VFx. VFx were associated with BMD spine, CSA and daily insulin dose.

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Proximal femur structural geometry changes in women with type 2 diabetes mellitus

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Objective
The aim of this study is to assess the geometric parameters of the femur in patients with type 2 diabetes mellitus (T2DM) without osteoporosis.
Materials and methods
There were examined totally 97 type 2 diabetic females. We included in our study 60 type 2 diabetic females without osteoporosis (T-score more than – 2.5 in axial skeleton), age: 56.9(53.8–60.9) yrs., duration of DM: 6.5(5–11.5)yrs., HbA1c: 8.6(6.9–10.1)%, BMI: 33.2(29.3–36.8) kg/m^2). The control group consisted of 45 women age: 56.2 (51.4–59.2), BMI: 31.6(27–36). Bone mineral density (BMD) was measured with DXA. Geometric parameters were determined using Advanced Hip Analysis program including hip axis length (HAL), cross-sectional moment of inertia (CSMI), cross-sectional area CSA and the femur strength index (FSI).
Results
Age, height and weight were not different between T2DM and controls. In group T2DM duration of menopause (T2DM: 6.5(3–10)yrs. vs controls: 5(2–8) yrs., $P=$ 0.009 respectively) was longer than in the control group. It has been established that the BMD (T-score) of the lumbar spine in patients with type 2 diabetes mellitus was lower in comparison with the control group (T2DM: T-score $-0.4((-1.3)-0.3)$ vs controls: T-score -0.1 $((-0.7)-0.6)$, $P=0.023$ respectively). However, the BMD of the proximal femur (T2DM: T-score $0.5((-0.35)-1.6)$ vs controls: T-score 0.6 (0.2–1.2), $P=0.578$ respectively) and femoral neck (T2DM: T-score $-0.25((-1)-0.5)$ vs controls: T-score -0.1 $((-0.5)-0.6)$, $P=0.097$ respectively) was comparable in both groups. T2DM females had lower CSMI (T2DM: 10169 (8777–11482) vs. controls 11106(9951–12803), $P=0.012$ respectively) and CSA (T2DM: 145.5(128–162.5) vs. control 151(141–167) $P=0.044$ respectively) compared with the control group. The HAL, FSI and neck-shaft angle of the femoral neck in both groups were comparable. With comparable anthropometric parameters and BMD of the femur these changes may indicate an increased cortical porosity of bone and a poor bone quality.
Conclusions
In female with DM 2 type hip geometric parameters CSA and CSMI were lower in comparison to the control group. The results of our own research indicate that hip geometry structural changes might potentially predispose to higher fracture risk in T2D females.

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P287

Case report: male adult with autosomal-dominant osteopetrosis

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Background
Osteopetrosis is a rare chronic bone disease with high bone mineral densitiy due to impaired osteoclast activity or development. Genetic mutations result in severe infantile (autosomal recessive, incidence 1:200,000) and less severe adult forms (autosomal-dominant osteopetrosis/ADO). The incidence is estimated at 1:20,000 for noninfantile forms. In adults osteopetrosis is often asymptomatic with increased risk for bone fracture. Treatment is symptom-based (e.g. calcium, cholecalciferol, calcitriol, red blood cell transfusion, interferon γ-1b, corticosteroids) since effective therapy is missing.
Case report
Twenty-seven year old male patient with a history of osteopetrosis for 9 years (self-employed photographer, working abroad, surfer/skater, smoker). Osteopetrosis was radiographically diagnosed in context with car accident and traumatic fracture of left clavicle. Further typical findings in spine ('sandwich vertebrae'), ribs, upper and lower limbs were detected in computertomography because of unclear abdominal pain and transient increased cervical lymph nodes 08/2017. Consultation of endocrinologist in 10/2017: No further bone fractures since 2008, slight pain of caudal left ribs after bruising, no routine medication. Diagnostic expert-based recommendations were taken from recent consensus guidelines from the osteopetrosis working group (Wu et al. 2017).
Results
Increased: tartrate-resistant acid phosphatase/TRAP5b: 54 U/l (1.4–6.1), BB isozyme of creatine kinase (CK-BB): 0.77 µkat/l (0.0 in healthy persons); bone mineral density (in g/cm^2: L1–L4 2.981; right femur 2.509; left femur 2.585) and T-score in DXA-scan (L1–L4 + 14.7; right femur + 10.9; left femur + 11.5 S.D.). Genetic analysis confirmed CLCN7 mutation (heterozygous) and thus autosomal dominant osteopetrosis type 2 (ADOII, Albers-Schönberg disease). MRI was cancelled due to metal near right orbita. Native computertomography of the brain excluded cranial (optic) nerve impingement but confirmed generalized thickening of the bone. Subspecial clinical complications (ophthalmology, hematology), pathologic alterations in renal ultrasonography and abnormal blood count (with differential), lactate dehydrogenase, serum calcium, intact parathyroid hormone, phosphorus, creatinine, 25-hydroxyvitamin D were not seen. Clinical controls and minimum laboratory (serum calcium, phosphorus, 25(OH)D, parathyroid hormone, blood count) were arranged half-yearly as recommended above (Wu et al. 2017). We clarified the patient of an increased risk of spontaneous and traumatic bone fracture with risky sports.
Conclusions
We established the patient's diagnosis ADO biochemically and genetically after first radiographic signs were confirmed one decade ago. Patients with osteopetrosis need to be monitored lifelong if appropriate in a multidisciplinary setting. Since epidemiological and clinical data is lacking publication of case reports is crucial.

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P288

Fragility index in type 2 diabetes for identification of patients with risk of osteoporotic fracture or prevalent fracture

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Introduction
Diabetes mellitus is associated with an increased risk of osteoporotic fractures, which leads to an increased risk of disability and frailty.
Aims
To assess the prevalence of frailty in type 2 diabetes and to analyze the relationship with bone mineral density (BMD) and Trabecular Bone Score (TBS), fracture risk and prevalent fractures.
Methods
We carried out a cross-sectional study of 75 diabetic patients (65 ± 7 years, 55.3% males). We collect data on clinical history, measured BMD and obtened trabecular bone score (TBS) by dual-energy X-ray absorptiometry (DXA) and software TBS InSight® respectively. We also estimated 10-year fractures risk using FRAX, FRAX adjusted with TBS and QFracture score. Finally, we conducted a validated fragility survey (Frail Scale).
Results
20% (*n*: 15) were considered fragile, 8% (n: 6) had densitometric osteoporosis and 13% (*n*: 10) had a history of fragility fractures. Frail scale was not related to the values of BMD or TBS. However, we found significant differences between fragile and non-fragile diabetic patients in the risk of major osteoporotic fracture (MOF) or hip fracture (HF) at 10 years in the FRAX score (MOF:: 4.7 4.2 vs 2.7 2.1 $P = 0.025$), FRAX score adjusted with TBS (MOF: 6.9 5.1 vs 3.8 3.1 $P = 0.015$; CF: 2 2.7 vs 0.7 1 $P = 0.009$) and QFracture score (MOF: 8.9 6.8 vs 4.9 3.8 $P = 0.012$; CF: 4.6 4.8 vs 2.3 2.3 $P = 0.018$). There were more patients with history of fractures in the group of fragile patients compared to non-fragile patients (35.7% vs. 8.2% $P = 0.006$).
Conclusion
Fragility index in type 2 diabetes mellitus is useful for identification of patients with risk of osteoporotic fracture or prevalent fracture.

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Calcium & Vitamin D metabolism

P289

Relationships between vitamins and lipids in the elderly

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Objective
In recent years, many studies have been conducted on the beneficial effects of vitamin D. Vitamin D have many important effects on calcium metabolism, skeletal system and also on different systems. Low serum vitamin D levels are predictors of type 2 diabetes mellitus, cancer, cardiovascular diseases, immunological diseases and even mortality. The relationships between vitamin D and cardiovascular diseases can be explained by the lipid-lowering effect of vitamin D. In many studies, there is general agreement that high serum vitamin D levels are associated with a healthy serum lipid profile. The aim of this study was to investigate whether vitamin D levels are associated with lipid levels in outpatients, and to compare the patients above and below 60 years of age.
Material and methods
The medical records of patients who applied to outpatient clinic between January 2015 and August 2017 were reviewed. 236 outpatients aged 19–88 years who had serum 25-hydroxyvitamin D (25(OH)D) levels, total cholesterol, LDL-cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride levels were included in the study. Patients' body mass index (BMI) was calculated. Overweight was defined as BMI (kg/m^2) between 25.0 and 29.9 and obesity was defined as BMI ≥30.0. Total cholesterol levels ≥200 mg/dl, LDL cholesterol levels ≥140 mg/dl and triglyceride levels ≥ 150 mg/dl were classified as high. HDL-cholesterol levels <40 mg/dl were defined as low. Serum 25(OH)D level <50 nmol/l, or <20 ng/ml, is an indication of vitamin D deficiency.
Results
This study was conducted with 236 outpatients aged 19–88 years. 46.2% of the study population were over 60 years old, 83.5% were female, 18.2% were normal weight, 50.4% were overweight and 31.4% were obese. 56.8% of the outpatients had high total cholesterol levels, 38.1% of had high LDL cholesterol levels and 30.1% of had high triglyceride levels. 14% of the outpatients had low HDL cholesterol levels. The prevalance of vitamin D deficiency was 49.6% (95% CI, 41–58%).
Conclusion
Patients with increased 25(OH)D levels in epidemiological studies; there was a significant decrease in total cholesterol, LDL cholesterol and triglyceride levels and an increase in HDL cholesterol levels (1–3). But, in our study, there was no statistically significant relationship between vitamin D deficiency and lipid profile in patients over 60 years and under 60 years of age. We planned to increase the number of patients.

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P290

Vitamin D and obesity

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Introduction
Vitamin D has been found to be associated with multiple chronic diseases, including diabetes mellitus type 1 and 2, rheumatoid arthritis, systemic lupus erythematosus and other autoimmune diseases. Low vitamin D levels have also been observed in patients with obesity.
Aim
The aim was to study vitamin D levels in patients with morbid obesity.
Methods
In a group of 32 patients with morbid obesity, BMI 41.77 ± 1.15 (mean ± SEM), range 27.76–51.99, weight 112.05 ± 3.18 kg, range 85–150 kg, $25(OH)D_3$ levels were measured. Observations were also performed in a group of 32 patients with BMI and weight in the normal range, within the same age group, of the same sex, serving as controls.
Results
In the group of obese patients $25(OH)D_3$ levels were 10.77 ± 0.51 ng/ml as opposed to 24.51 ± 1.35 ng/ml in the control group, ($P < 0.001$, Student's t test). A negative correlation was observed between $25(OH)D_3$ levels and BMI, standardized beta coefficient −0.87, $P = 0.001$. A negative correlation was also observed between $25(OH)D_3$ levels and weight, standardized beta coefficient −0.345, $P < 0.001$.
Conclusions
Very low vitamin D levels were observed in a group of morbidly obese patients. A negative correlation was observed between $25(OH)D_3$ levels, BMI and weight, meaning that low vitamin D levels were correlated with high BMI and weight. Vitamin D has been found to be a negative index of the acute inflammatory response (Quraishi *et al*, Curr Opin Clin Nutr 2012). We propose that vitamin D is a negative indicator of the inflammatory environment which characterizes morbid obesity.
Reference
Quraishi SA, Camargo CA Jr. Vitamin D in acute stress and critical illness. *Curr Opin Clin Nutr Metab Care* 2012;15:625–34.

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P291

Vitamin D deficiency and risk of metabolic syndrome

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Objective
Recent studies suggest that vitamin D deficiency could be a risk factor for metabolic abnormalities.
The aim of this study was to assess the relationship between 25(OH)D level and metabolic syndrome components.
Materials and methods
A total of 697 women from 30 to 55 y.o. were examined. Exclusion criteria were, clinically significant endocrine, renal, liver and GI diseases, regular insolation and intake of vitamin D and calcium supplementation. Anthropometric examination included height (m), weight (kg) and waist circumference (cm). Hemodynamic examination included systolic and diastolic blood pressure level (mmHg) measurement. Serum 25(OH)D level was performed using Abbott Architect 8000. Plasma glucose, serum lipids and insulin levels were performed using standard methods. Standard oral glucose tolerance test was performed if necessary. Insulin resistance index (HOMA-IR) were calculated. Metabolic syndrome diagnosed applying IDF criteria (2005).
Results
The study results showed that 90.7% of women had vitamin D deficiency or insufficiency, while 9.3% had normal vitamin D status. According to IDF criteria abdominal obesity was seen in 75.5%, impaired glucose tolerance (IGT) or type 2 diabetes in 33.3%, reduced HDL level in 32.2%, and hypertriglyceridemia in 23.4%. We found arterial hypertension in 26.6% of subjects. A total of 397 women were checked for metabolic syndrome, and it was diagnosed in 187 (47.1%) subjects. HOMA-IR was higher in subjects with metabolic syndrome (6.36 ± 0.81), in compared with subjects without metabolic syndrome (2.99 ± 0.13), ($P < 0.001$). Serum 25(OH)D level in women with or without metabolic syndrome did not differ (48.6 ± 1.8 & 51.1 ± 1.5 nmol/l, $P > 0.05$). We didn't find association between serum 25(OH)D level and HOMA-IR. Metabolic syndrome components risk was analyzed in women with different 25(OH)D level [OR, Cl95%]. We showed that vitamin D deficiency (25(OH)D < 50 nmol/l) was associated with an increased risk of abdominal obesity [2.23; 1.15–4.30] and low HDL [2.60; 1.04–6.49] compared to subjects with normal 25(OH)D level. IGT and type 2 diabetes risk was not significantly increased in women with vitamin D deficiency [1.07; 0.54–2.20]. Risk of metabolic syndrome did not differ in subjects with normal vitamin D status and insufficient/deficient women ($P > 0.05$).
Conclusions
Vitamin D deficiency could be associated with abdominal obesity, reduced HDL level and possibly increased risk of IGT or type 2 diabetes.

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Cardiovascular Endocrinology and Lipid Metabolism

P292

Effects of atorvastatin and ezetimibe therapy on LDL Cholesterol. A systematic review and meta-analysis of randomized controlled trial

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Background
Evidence has shown that the use of high doses of statins is associated with lower levels of LDL cholesterol and a decrease in cardiovascular events. Likewise, the use of high doses of statins may increase the risk of myopathy, elevation of liver enzymes, renal failure and cognitive alterations. We conducted a systematic review with a meta-analysis of all RCTs investigating the impact of atorvastatin and ezetimibe therapy on levels of LDL cholesterol vs high doses of atorvastin.
Methods
We comprehensively searched the databases of MEDLINE, EMBASE, and Cochrane from their dates of inception through October 2017. The inclusion criteria were published RCTs comparing change in LDL cholesterol between Atorvastatin/Ezetimibe (10/10 mg and 20/10 mg) administration and Atorvastatin in high doses (40 and 80 mg/day). We used a random-effects model and calculated pooled standardized mean difference (SMD) with 95% confidence intervals (CI) comparing change in levels of LDL cholesterol (mg/dl) between the atorvastatin/ezetimibe and atorvastatin in high doses groups.
Results
Three studies were included in the meta-analysis. Atorvastain/ezetimibe 10/10 mg and 20/10 mg compared with atorvastian in high doses (40 and 80 mg) group; the atorvastatin/ezetimibe therapy group had lower cholesterol LDL (SMD = −14.00 mg/dl, 95% CI: −14.23 to −13.83, P-value heterogeneity = 0.60, $I^2 = 0\%$). The rank correlation test of funnel plot asymmetry was z = 1.56, P-value = 0,11.
Conclusion
This meta-analysis of randomized studies demonstrates how atorvastatin/ezetimibe at low doses such as 10/10 mg and 20/10 mg vs atorvastatin 40 mg and 80 mg, was superior in reducing LDL cholesterol levels by 14 mg/dl, statistically significantly, and without publication bias (determined by the test of funnel plot asymmetry).

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Your patients say they do not tolerate statins? You can still lower their cardiovascular risk with red yeast rice supplementation

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Objectives
Main: To assess the effect on the 10-year risk of cardiovascular events (RCVE) of daily supplementation with a fixed combination of red yeast rice extract (250 mg), berberin 525 mg and coenzyme Q_{10} (50 mg) in patients with self-reported statin intolerance. Secondary: effects on anthropometric (BMI, SBP, DBP, HR) and laboratory (lipids, fasting glucose and HbA_{1C} in diabetic patients, eGFR, AST, ALT, GGT, CK); self-reported compliance and tolerance.
Methods
We recruited 30–75 year-old patients with LDL-cholesterol >130 mg/dl and triglycerides <300 mg/dl, without established coronary heart disease, cerebrovascular disease or heart failure, who had withdrawn statin therapy due to self-reported intolerance, without evidence of myolysis or hepatotoxicity. Data were obtained initially (>2 months after statin withdrawal) and after 3 months of therapy with the supplement. The study was open and uncontrolled. RCVE was estimated by the ASCVD Risk Estimator (AHA-ACC 2013). Statistical analysis were made with Kruskall-Wallis' H-test and Student's T-test.
Results
24 patients were recruited (age 59.2 ± 11.6, 17 women, 8 diabetic). 21 patients (87.5%) had adequate compliance ($>80\%$). No adverse effects were attributed to the supplement, and in no case AST, ALT or CK were >3xUNL.
RCVE: 12.4% → 9.3% (-25%, $P=0.0071$).
LDL-cholesterol (mg/dL): $166.3\pm31.2 \rightarrow 131.4\pm22.7$ (-21%, $P<0.0001$).
Total cholesterol (mg/dL): $248.6\pm48.4 \rightarrow 212.1\pm39.2$ (-15%, $P=0.0077$).
HDL-cholesterol (mg/dL): $41.4\pm8.3 \rightarrow 43.1\pm9.2$
Triglycerides (mg/dL): $204.5\pm69.8 \rightarrow 188.0\pm73.1$
AST (U/L): $39.7\pm11.7 \rightarrow 33.9\pm9.7$
ALT (U/L): $36.4\pm8.8 \rightarrow 32.7\pm9.2$
GGT (U/L): $67.6\pm18.7 \rightarrow 63.4\pm17.6$
CK (U/L): $87.4\pm16.8 \rightarrow 88.3\pm15.7$
BMI (kg/m^2): $29.6\pm5.2 \rightarrow 28.9\pm4.7$
SBP (mmHg): $144\pm11 \rightarrow 141\pm10$
DBP (mmHg): $83\pm9 \rightarrow 80\pm7$
HR (lpm): $78\pm8 \rightarrow 77\pm8$
Fasting glucose (mg/dL) in diabetic patients: $139\pm21 \rightarrow 132\pm17$
HbA_{1C} (%) in diabetic patients: $7.3\pm1.2 \rightarrow 6.9\pm1.0$
CKD-EPI eGFR (ml/min/1.73m^2): $68.5\pm11.3 \rightarrow 69.7\pm11.0$
Conclusions
The supplement was well tolerated in this group of hypercholesterolemic patients with self-diagnosed statin intolerance (without evidence of myopathy or liver disease); after 3 months the patients had marked reductions in total and LDL-cholesterol. and their RCVE was significantly reduced.

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Lobeglitazone, a novel thiazolidinedione, improves hepatic steatosis in diet-induced obese mice

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Although non-alcoholic fatty liver disease (NAFLD) patients are rapidly growing, there is not optimal therapy to improve NAFLD. NAFLD is strongly associated with insulin resistance. The peroxisome proliferator-activated receptor (PPAR) activator thiazolidinediones (TZD) is an insulin sensitizer, and have been focused as the drug for NAFLD. However, the TZD remain debate as drug of choice on NAFLD because of its conflicting results on the hepatic steatosis and fibrosis. Lobeglitazone could be more potent effects for improving insulin sensitivity in the T2DM patients. In the present study, we investigated the effects of new developed TZD, lobeglitazone on animal model with obesity-associated hepatic steatohepatitis, focusing on the lipid metabolism in liver. Lobeglitazone treatment for 4 weeks in high fat diet (HFD)-induced obese mice (HL group) improved the insulin resistance and glucose intolerance compared to HFD-induced obese mice (HU group). The gene related to hepatic gluconeogenesis also decreased by treatment of lobeglitazone. The liver of mice in HL group showed histologically reduced lipid accumulation with the lower plasma total cholesterol and triglyceride level. In addition, the HL group induced the significant decreases in the hepatic transcription levels of hepatic lipid synthesis, cholesterol biosynthesis and lipid droplet development genes, and the increase in the gene expressions of fatty acid β-oxidation. It suggested that lobeglitazone ameliorated the hepatic steatosis and recovered the hepatic lipid dysregulation. Liver with steatohepatitis increased not only the PPARγ, but also the phosphorylation of PPARγ at serine 273 (pS273) that leads to down-regulation of gene expression linked in insulin sensitivity. Lobeglitazone interestingly diminished the pS273 of PPARγ. It suggested that post-translational modification of PPARγ in liver by lobeglitazone might be one of underlying mechanisms for improvement of NAFLD. Collectively, lobeglitazone had potent beneficial effects on insulin sensitivity and hepatic steatosis through improvement of hepatic lipid metabolism. Our data revealed that the lobeglitazone shed the light on the novel therapy for the NAFLD.

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B-type natriuretic peptide: a biomarker of cardiovascular risk in type 2 diabetes.

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Background
Cardiovascular stratification and prevention in type 2 diabetic patients represent a major public health preoccupation in order to reduce their mortality. Several methods of detecting atherosclerosis have been developed such as biomarkers. The aim of this study was to evaluate the association between B-type natriuretic peptide (BNP) and cardiovascular risk (CVR) in type 2 diabetic patients.
Methods
We conducted a cross-sectional study in 71 type 2 diabetic patients (38 patients with at least one cardiovascular disease (CVD) and 33 patients without any CVD). Their CVR level was estimated using Framingham score (FS). All patients had BNP and high-sensitivity C-reactive protein (hs-CRP) measurements. BNP threshold was 10 pg/ml.
Results
The average level of BNP was 27.65 ± 31.95 pg/ml. It was significantly correlated with body weight ($r=0.3$, $P=0.01$), waist circumference ($r=0.2$, $P=0.03$), low HDL cholesterol ($r=-0.26$; $P=0.02$) and the number of CVR factors ($r=0.38$, $P=0.001$). It was significantly higher in patients with hypertension ($P<0.001$), dyslipidemia ($P=0.02$), metabolic syndrome ($P=0.009$), high CVR level ($P=0.04$), coronary heart disease (CHD) ($P=0.004$) and microangiopathy ($P=0.03$). High level of BNP was associated with an age ≥ 45 years for men and ≥ 55 years for women (hazard ratio [HR] 9.36, $P=0.03$), hypertension (HR = 7.27, $P<0.001$), metabolic syndrome ((HR = 3.64; $P=0.03$), high CVR level (HR = 6.6, $P=0.01$), CHD (HR = 2.8, $P=0.04$), diabetic retinopathy (HR = 3.14, $P=0.03$) and diabetic nephropathy (HR = 3.12, $P=0.03$). BNP had higher sensibilities (se) and specificities (sp) than Hs-CRP as a marker of high CVR level (se: 62.3% vs 41.7%; sp: 80% vs 52.6%, respectively).
Conclusion
Our results demonstrated significant associations between BNP, high CVR level, CHD and microangiopathy in type 2 diabetic patients. However, prospective controlled studies including a large population are needed to confirm these results.

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Relationship between the triglyceride glucose index and the presence and fibrosis of nonalcoholic fatty liver disease in Korean adults

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Background
Recently, the triglyceride glucose (TyG) index has been considered a surrogate marker of insulin resistance. Insulin resistance is a well known pathogenic factor in nonalcoholic fatty liver disease (NAFLD). However, few studies have investigated the relationship between the TyG index and liver fibrosis in subjects with NAFLD. Thus, we investigated the relationship between the TyG index and liver fibrosis in Korean adults.
Methods
In total, 5158 participants who underwent ultrasonography in a health promotion center were enrolled. Anthropometric profiles and multiple metabolic risk factors were measured. The TyG index was calculated as ln [fasting triglycerides (mg/dl) $\times$ fasting glucose (mg/dl)/2], and the insulin resistance index of homeostasis model assessment (HOMA-IR) was estimated. NAFLD was diagnosed by ultrasonography, and degree of liver fibrosis was assessed by NAFLD fibrosis score (NFS). Significant liver fibrosis was defined as NFS ≥ -1.5.
Results
All subjects were stratified into four groups based on their TyG indices. Significant differences were observed in metabolic parameters among the groups, and the prevalence of NAFLD and liver fibrosis by NFS significantly increased with increasing TyG index. When classifying the severity of NAFLD into three groups, there was a significant correlation between the severity of NAFLD and the TyG index. In the logistic regression analysis after adjustment for multiple risk factors, the odds ratio for the prevalence of liver fibrosis, when comparing the highest and lowest quartiles of the TyG index was 1.92 (95% CI: 1.46–2.53; *P* for trend < 0.01); the odds ratio for the prevalence of liver fibrosis, when comparing the highest and lowest quartiles of HOMA-IR was 2.92 (95% CI: 1.12–2.40; *P* for trend <0.01).
Conclusion
There is a significant association between the TyG index and liver fibrosis of NAFLD, but HOMA-IR was superior to TyG index for predicting liver fibrosis in NAFLD patients.

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Adropin concentration correlates with selected anthropometric and biochemical parameters – preliminary report

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Adropin, hormone playing an important role in carbohydrates and lipids metabolism, improves mainly the glucose homeostasis. It could also play a protective role in pathogenesis and development of cardiovascular diseases. The purpose of the study was to assess the adropin concentration and some parameters of nutritional status (BMI, WHtR, BAI, VAI) as well as biochemical parameters (fasting glucose and insulin, and lipid profile). 25 patients (84% of group was women, $n=21$) without any carbohydrate metabolism disorders, diagnosed at endocrinology department because of other reasons were included to the study. The exclusion criteria were any glucose metabolism disorders (diabetes mellitus, insulin resistance, glucose intolerance, fasting glucose impairment) or medications influence glucose concentration and metabolism (glucocorticosteroids, hypoglycaemic drugs, etc.). The data were statistically analyzed by STATISTICA. $\alpha=0.05$. The median serum levels of adropin concentration was 1387.9 pg/ml (1187.4–1655.7 pg/ml). There was observed a negative correlation between WHtR index and adropin concentration ($R=-0.41$, $P=0.0385$) and a positive correlation between adropin level and HDL cholesterol ($R=0.41$, $P=0.04$). In the next step the examined group was divided into two subgroups concerning the cardiovascular risk defined by WHtR index (above 5 – high risk and below 5 – low risk). At that step there was no significant differences observed between serum concentration of adropin concerning into two groups defined by WHtR index (respectively 1413.1 vs 1512.2, $P=0.4598$). Concerning glucose metabolism parameters there was no correlation observed between adropin level in relation to fasting glucose and fasting insulin ($P>0.05$). The following step was to compare adropin concentration to the certain parameters of nutritional status. There was observed no correlation between BMI, BAI, VAI indexes and adropin levels ($P>0.05$). Adropin via regulation fat accumulation, lipid metabolism and HDL -cholesterol concentration could present a protective role in cardiovascular diseases. To strengthen the results an enlargement of study group is required.

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Silent myocardial ischemia in type 2 diabetes patients with ischemic heart disease

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Objective
The prevalence of silent myocardial ischemia (SMI) is more frequent in diabetic patients and is associated with a worse prognosis. It has been known that diabetes is a major cardiovascular risk factor; it often leads to severe cardiovascular complications, and coronary artery disease (CAD) is the main cause of death in diabetic patients. The aim was to examine the prevalence and duration of SMI in type 2 diabetes (DT2) patients with ischemic heart disease (IHD).
Materials and methods
180 patients both sexes with type 2 diabetes aged 56.56 ± 11.07 years were studied. All patients were divided into 4 groups: 1 – 50 (27.8%) patients with stable angina pectoris (SAP), 2 – 50 (27.8%) patients with SAP and DT2, 3 – 50 (27.8%) DT2 patients and 4 – 30 (16.6%) healthy control group. In all patients 24-h ECG Holter monitoring was carried out.
Results
We found significant differences in duration of episodes of painful and silent myocardial ischemia between groups. Patients with SAP and DT2 had a long duration of SMI than patients with SAP without DT2 ($P=0.019$). There were not significant differences between 1 and 2 groups in the number of patients with painful myocardial ischemia (PMI) ($P=0.06$). Episodes of PMI were not recorded among patients of group 3.
Conclusions
Silent myocardial ischemia is more often in patients with DT2 and IHD due to autonomic neuropathy.

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PCSK9 inhibitors as an add on for the treatment of dislipemia in real clinical practice

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Introduction and objectives
The treatment with monoclonal antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9) is a new group of drugs that allows us to reach the therapeutic targets of low density cholesterol (LDL-c) in patients intolerant to statins or those who despite treatment with maximum doses of them do not obtain a proper lipid control.
Material and methods
We performed a descriptive observational study. We include all patients with hypercholesterolemia who started treatment with iPCSK9 at the Virgen de la Victoria Hospital of Malaga. We analyzed the clinical characteristics, indication

for iPCSK9 treatment and changes in LDL-c levels at the first visit and after 6 months of treatment. The diagnoses included are: Heterozygous Familial Hypercholesterolemia, 23 patients (66%); Mixed Dyslipidemia, 8 patients (23%); and Polygenic Hypercholesterolemia, 4 patients (11%).
Results
We analyzed data from 35 patients with mean age 60 years (±10 years), 57% males. They had associated comorbidities: 20% were active smokers, 63% had high blood pressure, 11% had diabetes mellitus, 49% were obese and 63% have had a cardiovascular event. Regarding the treatment prior to the addition of iPCSK9: 77% were on statins plus ezetimibe at maximum doses; 3% were only statins, 11% were on ezetimibe and 9% were without treatment because of intolerance. Before starting iPCSK9 treatment: Total cholesterol was 256 mg/dl (±90), LDL-C was 161 mg/dl (±47), was HDL-C 51 mg/dl (±14) and triglycerides 165 mg/dl (±105). 48% ($n=17$) of patients presented intolerance to maximum doses of statins (myalgias and gastrointestinal symptoms). They received iPCSK9 as follows: Evolocumab 140 mg 13 patients (34%) and Alirocumab 22 patients (63%); 14% Alirocumab 75 mg and 48.6% Alirocumab 150 mg. The mean LDL-C levels after the first six months of treatment was 74±40 mg/dl (55% reduction compared to the initial LDL-C, $P=0.000$). In the analysis by subgroups: Alirocumab reduced 46% and Evolocumab 65%, this reduction was statistically significant with respect to the initial parameters but without finding differences between the two drugs ($P=0.092$). Two patients presented mild adverse reactions and other three were hyper responders, None had to suspend the treatment for these reasons or presented new cardiovascular event.
Conclusions
The iPCSK9 are an effective and safe treatment in patients with high cardiovascular risk and high levels of c-LDL, at least in the first 6 months after administration without differences between both options.

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P300

Treatment adherence through an Integral Care Program for patients with Metabolic Syndrome in Central Mexico

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Introduction
The Metabolic Syndrome (MS) is a cluster of risk factors that are related to cardiovascular disease. In Mexico, the prevalence of MS in adults according to the ENSANUT 2012 is 41%, and it has become a public health problem making it necessary to implement strategies for its management at the lowest cost possible that could encourage adherence to treatment.
Objective
To evaluate the effectiveness of a comprehensive care program to achieve an increase in the adherence to treatment through the change of behaviors in lifestyles.
Methods
Prospective and experimental study involving 34 adults (32 women – 94% and 2 men – 6%) with MS using the armonized criteria, from rural areas of central Mexico who had public health services, age of 54.5+10.5 years, 4 years of average schooling, occupation as housewives (60%) and farmers (40%). They underwent a comprehensive care program which included a workshop on food preparation, aerobic exercise and strength training (180 min/week), guidance on the disease and its complications for six months. Adherence to treatment was evaluated in 5 domains: diet, exercise, pharmacological consumption, prevention of complications and social support through the Transtheoretical Model. Descriptive statistics and χ^2 were used to evaluate the differences in the percentages of the 5 domains, with the Statistica V13 software. The protocol was approved by the institutional ethics committee.
Results and discussion
Statistically significant difference in the percentages of treatment adherence was found in the 5 domains evaluated comparing the beginning versus the end of the maneuver as follows: diet 5.8% to 39.7% ($\chi^2=31.3$, $P=0.0000$), exercise 25% to 50% ($\chi^2=22.6$, $P=0.0000$), pharmacological use 41.1% to 48.5% ($\chi^2=3.98$, $P=0.04$), prevention of complications 12.1% to 24.4% ($\chi^2=4.99$, $P=0.02$) and social support 13% to 26% ($\chi^2=10.1$, $P=0.001$). Despite the increase in the observed percentage of attachment, treatment adherence was not found to an optimum degree in the group studied; is necessary to reinforce the acquired behaviors by supporting the health system that the population has, since changes in lifestyle were encouraged.
Conclusion
The Comprehensive Care Program was effective in increasing treatment adherence in patients with MS residing in central Mexico. This low-cost maneuver encourages the actions of the public health system in the treatment of this pathology.
Keywords. Metabolic syndrome, adherence to treatment
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P301

Searching the best feeding habits to improve atherogenic dyslipidemia and inflammatory activity in patients with psoriatic arthritis

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Introduction
There is solid epidemiologic evidence linking psoriasis and psoriatic arthritis (PsA) to cardiovascular risk factors and an increased risk for developing cardiovascular diseases. Despite this, dietetic advice is not routinely performed in clinical practice in patients with inflammatory arthropathies and the potential effect of diet on metabolic profile and inflammatory activity is few studied in these patients. This research aims to describe dietetic habits of a cohort of patients with PsA and to investigate the potential influence of these habits on metabolic profile, particularly on atherogenic dyslipidemia, and inflammatory activity.
Methods/design
In this cross-sectional study, forty out-patients with PsA were included. Qualitative and quantitative characteristics of food intake were recorded in all patients. According to characteristics of diet, patients were classified in three groups: High protein, balanced or high carbohydrate diet. Demographic data and metabolic profile were collected. Atherogenic index was calculated as marker of cardiovascular disease. Inflammatory activity was measured by erythrocyte sedimentation rate (ESR), reactive C protein (RPC) and disease activity score (DAS 28).
Results
Balanced, high carbohydrate and high protein diet were followed by 54%, 30% and 17% of the cohort respectively. Patients with high protein diet had lower total cholesterol levels when compared to those with a balanced or a high carbohydrate diet (177.1±31.6 mg/dl vs 215.8±37 mg/dl vs 200.5±27.2 mg/dl respectively; $P=0.037$). Atherogenic index was lower in these patients (1.8±1.3 vs 2.4±1.1 vs 2.6±1.3; $P=0.032$). Fish was the main source of proteins in high protein diet group. With regard to inflammatory indexes, ESR and RCP were lower in patients with high protein diet, but DAS 28 score was lower in high carbohydrate diet group, but significant differences were not reached.
Conclusions
Metabolic benefits, at least on lipid profile, are more likely to be found in patients with PsA that follow a high protein diet when fish is the main source of protein intake, resulting in potential cardiovascular benefits linked to a lower prevalence of atherogenic dyslipidemia. However, diet habits were not linked to lower inflammatory activity. Further prospective studies are needed to verify our observation.

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Worse MELD score is linked to a higher rate of metabolic syndrome in HIV/HCV co-infected patients on highly active antiretroviral therapy

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Introduction
The prevalence of metabolic syndrome (MetS) is increasing in patients with HIV infection on highly active antiretroviral therapy (HAART). Additionally, HCV coinfection is common among HIV patients in our area. It is widely known MetS impacts on the liver in different ways but relationship between both MetS and liver function is few studied in HIV/HVC co-infected population.

Methods/design
Cross-sectional study including 35 HIV/HVC co-infected patients. Patients with significant ascites were excluded for analysis. All patients were screened for visceral obesity, dyslipidemia, hyperglycemia, and hypertension. Abdominal circumference was also measured. NCEP-ATP III criteria were used to define MetS and Model for End-Stage Liver Disease (MELD) score was calculated for every patient. Patients were divided into two groups according to median MELD score. Continuous variables are presented as mean and standard deviation or as median and interquartile range based on data distribution. Categorical variables are presented as frequencies.
Results
Prevalence of MetS was higher among patients with higher MELD score (100% vs 27.6%; $P=0.002$). When every individual component of MetS was analyzed, high abdominal circumference was more prevalent among patients with higher MELD score (54.5% vs 14.3%; $P=0.003$) but no other showed significant difference between groups. Patients with higher MELD score also had lower levels of HDLc (38 (33–45) vs 46 (39–58) mg/dl; $P=0.032$). Among patients with higher MELD score, no significant differences were observed according to LDLc (89.9±25.8 vs 107.2±37.2 mg/dl; $P=0.08$) tryglicerides levels (114 (83.2–198.2) vs 129 (93–185) mg/dl; $P=0.37$), systolic blood pressure (121 (113.2–130) vs 120 (107–130) mm Hg; $P=0.20$) or dyastolic blood pressure (80 (74–82) vs 77 (70–80) mm Hg; $P=0.08$).
Conclusions
A worse liver function is linked to development of MetS in HIV/HCV co-infected patients on HAART and therefore, related to higher cardiovascular risk. Abdominal circumference and lipid profile are major determinants for the higher rate of MetS observed in these patients. Due to the cross-sectional nature of our observation, further follow-up studies are needed to delucidate cause-effect.

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P303

Improved lipid profile and cardiovascular risk factors after bariatric surgery

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Background
Bariatric Surgery (BS) is an effective treatment for the metabolic control of obese patients. One of its purposes is to improve the lipid profile and reduce cardiovascular risk.
Aims
• To determine the changes in lipid profile and other cardiovascular risk factors before and one year after BS.
• To assess differences in lipid parameters depending on the surgical procedure used.
• To assess pre and post BS admissions in the cardiology ward.
Methods
Retrospective observational study of 418 patients who underwent BS from 1998 to 2017. Registered variables were gender, age, BMI, type of surgery, total cholesterol, HDL, triglycerides, blood pressure, blood glucose and HbA1c, baseline and one year after surgery (expressed as median and interquartile range) and compared according to the surgical procedure. The number and reasons for admission in cardiology before and after BS for patients in our health area was also recorded.
Results
Of the 418 patients, 76.3% were women. 88% underwent malabsorptive-restrictive procedures and 12% underwent pure restrictive procedures. Median age and BMI were 44.98 (16.33) years and 46.94 (8.97) kg. Levels of cholesterol, HDL, triglycerides, systolic blood pressure, diastolic blood pressure, blood glucose and HbA1c were 192 (148.5) mg/dl, 45 (15.75) mg/dl, 119 (80.75) mg/dl, 140 (18.75) mmHg, 90 (14.75) mmHg, 98.5 (29, 75) mg/dl, 5.8 (1.08)% respectively, and were reduced significantly one year after BS ($P<0.001$) to: 142.5 (46.75) mg/dl, 48.5 (16,75) mg/dl, 97 (61) mg/dl, 90 (14.75) mmHg, 75.5 (18.75) mmHg, 82.5 (12) mg/dl, 5.05 (0.5)%. Improvement in cholesterol, diastolic blood pressure and Glu/HbA1c was higher for malabsorptive procedures ($P<0.05$). Among patients in the area of León, 2% had an admission in the cardiology ward before BS (50% were ischemic). 4% were admitted after BS: 8.3% due to ischemic causes and 66.6% because of arrhythmias.
Conclusions
Bariatric surgery significantly improves lipid parameters and cardiovascular risk factors in one year, especially with malabsorptive procedures. The rate of admission for ischemic heart disease is lower than the reported to general population in our community (5.7/10000 population vs 8.25/10000 inhabitants in 2014 in the community of Castilla y León).

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P304

Efficacy and safety of proprotein convertase subtilisin/kexintype nine inhibitors in real life experience

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Introduction
PCSK9 inhibitors (iPCSK9) have previously been evaluated through controlled clinical trials showing up to 60% reduction in LDL cholesterol concentrations. However, we still do not have enough data regarding the real life experience of the treatment.
Objectives
1) Describe patients with hypercholesterolemia treated with iPCSK9 in clinical practice.
2) Evaluate treatment efficacy and safety.
Methods
Retrospective observational study. Inclusion criteria: patients treated with iPCSK9 at the Alicante University General Hospital. Primary end point: changes in LDL cholesterol 3 and 6 months after the start of iPCSK9. Secondary end point: changes in total cholesterol (TC), HDL cholesterol and triglycerides (TG). Other variables: Occurrence of adverse events. Statistical analysis: descriptive (mean ± S.D., median [P25–P75]), Wilcoxon; $P<0.05$; SPSS v22.0.
Results
24 patients (50% women, age 60±12 years, BMI 27±3 kg/m^2). 62.5% heterozygous familial hypercholesterolemia, 58% onset cardiovascular disease, 21% both. At baseline 66% patients were taking combination ezetimibe-statins therapy (21% rosuvastatin 20 mg/d, 4% rosuvastatin 10 mg/d, 13% rosuvastatin 40 mg/d, 21% atorvastatin 80 mg/d), 21% statin therapy (8% rosuvastatin 20 mg/d, 8% atorvastatin 80 mg/d), 4% monotherapy with ezetimibe 10 mg/d. Evolocumab 140 mg was prescribed in 62.5% of cases and alirocumab 75 mg in 37.5%. Primary end point: 50% reduction in LDL [16–61%] at 3 months, 55% [42–74%] at 6 months ($P<0.01$). Secondary end point: 38% reduction in TC [21–44%] at 3 months, 41% [21–44%] at 6 months ($P<0.01$). Non-significant 7% decrease in TG at 3 months, 3% at 6 months. There were also no significant changes in HDL. 5 of the 24 patients (21%) presented mild adverse events: 1 recurrent respiratory tract infections, 2 flu-like syndrome, 1 hypertransaminasemia, 1 pruritus. None of them demonstrated increase in plasma glucosa levels, or showed neurocognitive symptoms.
Conclusion
In short-term real life studies, the addition of PCSK9 inhibitors to their previous treatment leads to improvement in metabolic control with an adequate safety profile.

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P305

Plasma insulin levels in patients with the different severity of atherosclerotic lesions of coronary arteries

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Introduction
There is growing body of evidence that insulin resistance and hyperinsulinemia can contribute to development and accelerate the progression of atherogenesis of large arteries. However, an association between the severity of angiographically

confirmed atherosclerotic lesions of coronary arteries and the levels of insulin in the plasma in patients with ischemic heart disease (IHD) without history of diabetes mellitus or dysglycemia was not properly examined. The aim of the study was to investigate the plasma insulin levels in patients with clinically and angiographically confirmed IHD and different severity of atherosclerotic lesions of coronary arteries.

Materials and methods

We examined 78 patients with IHD without history of diabetes mellitus or impaired glucose tolerance (aged 61.5 + 9.2 years, BMI – 29.5 + 5.1 kg/m^2). All studied patients underwent stress test, coronaroventriculography and oral glucose tolerance test. The blood was collected at fasting and 2 h after glucose ingestion. Insulin levels were determined in all blood samples by radioimmunosorbent method (ELISA) along with plasma glucose measurements.

Results

All studied patients with IHD were divided to three groups according to the number of occluded coronary arteries (with atherosclerotic lesions located in 1, 2 and 3 coronary arteries, respectively). None of the studied patients had type 2 diabetes mellitus or impaired glucose tolerance based on the results of oral glucose tolerance test. The mean plasma glucose levels were not significantly different between all three groups of patients studied either at fasting or 2 h after ingestion of glucose during oral glucose tolerance test. Also, there was no elevation of glycated hemoglobin levels in all patients studied. It was found that fasting plasma insulin levels were significantly elevated in patients with IHD and multiple atherosclerotic lesions which expanded to 2 or 3 coronary arteries compared to patients with 1 occluded artery. The insulin levels at fasting were 19.1 + 1.16, 24.1 + 2.28, 25.0 + 1.64 μMU/ml in patients with 1, 2 or 3 occluded coronary arteries, respectively, $P < 0.05$ for comparisons between insulin levels in subjects with 2 and 3 damaged arteries compared to 1 artery. The similar trend was found in plasma insulin levels 2 h after administration of glucose.

Conclusions

Hyperinsulinemia as the reflection of insulin resistance is related to the more severe angiographically documented atherosclerotic lesions of coronary arteries in patients with IHD. We may speculate that hyperinsulinemia can play a role in the progression of atherosclerosis of coronary arteries.

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A multi-disciplinary approach to the management of NAFLD improves both liver and metabolic health and is cost effective

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and is tightly associated with type 2 diabetes (T2DM), the principal risk factor for disease progression, liver failure and cardiovascular complications. At present there are no licensed therapies and management aims to optimise metabolic risk factors through weight loss, and pharmacological interventions for diabetes and cardiovascular disease. A multidisciplinary approach involving hepatologists and diabetologists working alongside allied health professionals providing structured lifestyle advice is advocated, although objective evaluations of this approach are currently limited.

Objective

We have undertaken a retrospective study to determine the impact of a large, tertiary centre, multidisciplinary metabolic hepatology clinic. Detailed liver, cardio-metabolic and related health parameters including surrogate markers of metabolic syndrome, cardiovascular risk and liver disease were evaluated in addition to a pilot health economic analysis.

Results:

165 patients with NAFLD without hepatic co-morbidities and excluding those undergoing bariatric surgery, were followed from referral until latest review. All patients attended ≥2 times between 2014 and 2017. Median follow-up period was 13 months (2–34). At baseline, 29% had liver cirrhosis and 59% had T2DM. At follow-up, weight decreased by 3.3 kg (3.4%, $P = 0.0005$) and was associated with significant improvements in liver chemistry (alanine aminotransferase, ALT: −11 IU/l, 21%, $P < 0.0001$), and total cholesterol (−0.7 mmol/l; 14%, $P = 0.0023$). Median HbA1c fell (1.5 mmol/mol, 3.1%, $P = 0.0045$), with reduction most marked in those with poorly controlled T2DM (HbA1c >58 mmol/mol at baseline: −14 mmol/mol, 18%, $P < 0.0001$). Overall, there was a 6.4% reduction in 10-year cardiovascular risk (QRISK3, aged-match, $P = 0.0085$). Finally, median liver stiffness, measured using transient elastography as a surrogate of fibrosis, decreased by 1.3 kPa (14%, $P = 0.0097$). Preliminary economic analysis of our multidisciplinary approach using the UKPDS Outcomes Model indicated an improvement in quality adjusted life expectancy alongside a reduction of costs of diabetes complications if health improvements were maintained. Importantly, these costs fell well below the accepted UK cost-per-QALY (quality adjusted life year) threshold of £20,000 for commissioning of health interventions, suggesting a cost-effective clinical management strategy.

Conclusion

Our results demonstrate that patients with NAFLD managed through a multidisciplinary approach derive significant clinical improvements in liver and cardio-metabolic health. Patients with poorly controlled T2DM, demonstrated the largest improvement in HbA1c of a magnitude known to reduce complications which may potentially confer good benefit to patients in slowing NAFLD progression. Furthermore, our pilot economic data suggest that this approach may also be cost-effective.

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A case of combined dyslipidemia with two different defined genetic alterations

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Background

There are plenty of primary genetic or secondary causes for both hypercholesterolemia and hypertriglyceridemia. Two different genetic causes in one patient does not generally come to mind in first place.

Aim

We report a case who has two genetic alterations as a cause of hypercholesterolemia and hypertriglyceridemia.

Case report

62 year-old male referred because of high serum lipid levels. He had no active complaint. There were type 2 DM, hypertension for 15 years and an ischemic cerebrovascular event 10 years ago in his medical story. His medications included metformin, valsartan and ASA. Statin therapy was started 5 years ago but has not been using it for two years. He had no family history for pancreatitis, early-onset coronary heart disease and cerebrovascular disease. Tendon or tuberous xanthoma, xanthelesmas were not present in his physical exam. Laboratory analysis showed that LDL-C: 248 mg/dl (60–130) Total Cholesterol: 393 mg/dl (110–200) HDL-C: 63 mg/dl (40–60) Triglyceride: 506 mg/dl (<150). Fasting blood glucose was 98 mg/dl, HbA1c: 5.9%. His kidney, liver and thyroid function tests were normal. ECG, echocardigram and carotid arterial doppler USG revealed no pathology. Abdominal USG showed grade 2 hepatosteatosis. According to genetic testing for familial causes for hypercholesterolemia and hypertriglyceridemia; we found a heterozygous change in LDLR gene (c.1706-10G>A) which is accepted as a mutation for familial hypercholesterolemia. We also found a heterozygous change in APOA5 gene p.Ser19Trp (c.56 C>G) which is suggested for an increasing in tendency for hypertriglyceridemia.

Conclusions

Although very rare, different genetic alterations can be together in patients with high LDL-C and high triglyceride levels.

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Soluble ST2, a promising cardiovascular biomarker, is associated with parameters of glucose and bone metabolism in subjects at cardiovascular risk

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Introduction
Soluble ST2 (sST2) is the truncated soluble form of the ST2 receptor in the circulation. It is a decoy receptor of IL-33 and thereby inhibits the effects of IL-33/ST2 signaling. Elevated levels of sST2 have been associated with various adverse cardiovascular outcomes. Recently, potential associations of sST2 with obesity and type 2 diabetes mellitus (T2DM) have been described in the general population. In this study, we determined possible cross-sectional associations of sST2 with surrogate parameters of cardiovascular and metabolic risk in vitamin D-deficient subjects with and without T2DM.
Methods
Serum sST2 levels were measured (by Human St2/IL-33 R Quantikine ELISA Kit; R&D Systems) in 174 hypertensive, vitamin D deficient [25(OH)D $<$ 30 ng/ml] participants of the Styrian Vitamin D Hypertension Trial (NCT02136771). After assigning cardiovascular characteristics and parameters of bone and glucose metabolism to the respective quartiles according to sST2 concentrations, we used ANOVA, Jonckheere-Terpstra tests and chi-square tests to determine the presence of significant trends. In addition, a multiple regression model was constructed after adjusting each of the parameters for age and gender.
Results
We found significant trends across quartiles of sST2 concentrations for (BMI; $P=0.024$), plasma glucose ($P < 0.001$), insulin ($P < 0.001$), haemoglobin A1c (HbA1c; $P=0.001$), HOMA-IR ($P < 0.001$), T2DM prevalence ($P=0.007$), gender ($P < 0.001$), gamma-glutamyl transferase (GGT; $P < 0.001$), mean 24-h systolic blood pressure ($P=0.016$), total cholesterol ($P=0.001$), HDL ($P=0.002$), LDL ($P=0.004$) and osteocalcin (OC; $P=0.001$), while C-reactive protein, pulse wave velocity, mean 24-h diastolic blood pressure, NT-proBNP, eGFR, triglycerides and time since T2DM onset showed no significant association. In a multiple regression model we found HOMA-IR to be the only significant predictor of sST2 concentrations (adj. $R^2 = 0.124$, $\beta=0.359$, $P<0.001$) among the parameters included in the study.
Discussion
We found higher concentrations of sST2 positively associated with parameters of glucose and bone metabolism in vitamin D deficient subjects at cardiovascular risk, with HOMA-IR showing the strongest association. The findings of our study provide additional information on the emerging role of sST2 in obesity and T2DM, while uncovering a possible link to bone metabolism via osteocalcin.

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P309

Comparison of inflamatory parameters, lipid profile and clinical values in patients with clinical and subclinical hypothyroidism

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Aim
In this study, we aimed to perform a comparative evaluation of lipid profile, inflamatory markers, clinical parameters, which are related to cardiovascular diseases, and measurements of carotid intima media thickness (CIMT), which is considered to be an indicator of cardiovascular diseases, in patients with overt and subclinical hypothyroidism, all of which have been studied separately in differen studies.
Methods
Patients older than 18 years old, who admitted to the Endocrinology outpatient clinic, with the diagnosis of hypothyroidism (overt and subclinical) were enrolled into the study. Antropometric and serum lipid, hs-CRP, ESR and CIMT of the patients were studied.
Results
Totally 63 patients were included in the study. 55 (87%) of them were females and 8 (13%) of them were males. Mean ages of patients were 34.4 ± 11.9 years. 51 (81%) of patients were diagnosed as subclinical hypothyroidism, and 12 (19%) of them were diagnosed as overt hypothyroidism. Mean BMI was 27.1 ± 5.6 kg/m^2. Systolic and diastolic blood pressures were within normal limits.Mean, ESR was 12.6 ± 9.1 mm/h, hs-CRP was 4.3 ± 1.5 mg/l, total cholesterol was 195 ± 43 mg/dl, LDL cholesterol was 115.3 ± 36.1 mg/dl, Lp (a) was 17.8 ± 20.3 mg/dl and CIMT was 0.66 ± 0.17 mm. Patients were divided into two groups as subclinical and overt hypothyroidism which were similar in terms of age, gender. Mean CIMT measurement was higher in the overt hypothyroidism group than the subclinical group ($P=0.11$). Mean CIMT of both groups were higher than age-sex matched healthy population.
Conclusion
Our study group is at risk for early atherosclerosis and cardiovascular diseases because our patients are overweight and their levels of LDL cholesterol and hs-CRP and CIMT values are higher. This risk is higher in the overt hypothyroid group.

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P310

High levels of sclerostin are related to cardiovascular mortality

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Introduction
Cardiovascular disease (CVD) is a health issue, worldwide, particularly in individuals with diabetes. The identification of CVD biomarkers can improve risk stratification. Sclerostin is a modulator of the Wnt/β-catenin signalling pathway in different tissues, and has recently been linked to vascular biology.
Objectives
Our objective was to evaluate the relationship between circulating sclerostin levels and cardiovascular and non-cardiovascular mortality in individuals with and without type 2 diabetes.
Material and methods
A cohort of 130 participants (mean age 56.8 years; 75 with type 2 diabetes; 46 with prevalent CVD), were followed-up for 7 years. Time to death (both of cardiovascular and non-cardiovascular causes) was assessed to establish the relationship between sclerostin and mortality. Serum sclerostin levels were measured at the baseline.
Results
Serum sclerostin concentrations were significantly higher in patients with prevalent CVD ($P<0.001$), and independently associated with cardiovascular mortality ($P=0.008$), showing sclerostin to be a stronger predictor of mortality than other classical risk factors (area under the curve = 0.849 vs 0.823). The survival analysis showed that an increase of 10 pmol/l in the serum sclerostin level resulted in a 31% increase in cardiovascular mortality. No significant association was observed between sclerostin levels and non-cardiovascular mortality ($P=0.346$).
Conclusions
High sclerostin levels are related to mortality due to cardiovascular causes. The clinical implication of these findings is based on the possible use of serum sclerostin as a new biomarker of cardiovascular mortality risk in order to establish preventive strategies.

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P311

Lipid profile after pregnancy in women with gestational diabetes mellitus

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Aim
The aim of our study was to describe the lipid profile of Tunisian women after pregnancy with gestational diabetes mellitus (GDM) and to analyze the influence of maternal age, insulin requirement and postpartum glycemic status on lipoproteins changes after pregnancy.
Methods
We conducted a cross-sectional study among pregnant women who were referred to the national institute of nutrition for management of GDM. The lipid profile included total cholesterol (TC), HDL-C (High density lipoprotein-C) and triglycerides (TG). Pregnant women with prior diabetes or prior known dyslipidemia or thyroid disorders were excluded. Subgroups analyses were performed according to categories of maternal age (<35 years versus ≥ 35 years), insulin requirement (yes versus no) and postpartum glycemic status (normal HGPO, abnormal HGPO).
Results
After pregnancy (23 ± 7.5 Weeks post-partum), mean triglyceride, total cholesterol and HDL cholesterol levels were 1.02 ± 0.68 mmol/l, 1.3 ± 0.23 mmol/l and 5 ± 1.18 mmol/l respectively. An average significant decrease of $43.4 \pm 40.8\%$ in triglycerides levels ($P=0.002$), of $15.4 \pm 14.9\%$ in total cholesterol ($P=0.001$) and of $14 \pm 26.6\%$ in HDL cholesterol ($P=0.016$) was observed. After pregnancy, no woman had isolated hypertriglyceridemia (higher than 1.7 mmol/L), 15% had isolated hypercholesterolemia (higher than 5.2 mmol/L), 30% had mixed hyperlipidemia and 45% had low HDL-C (lower than 1.7 mmol/L). No significant differences in lipids variation were observed according to postpartum glycemic status neither according to maternal age. Insulin-treated patients showed a significant lower decrease of total cholesterol ($P=0.035$).
Conclusions
Dyslipidemia is a persistent problem in women with gestational diabetes mellitus after pregnancy. Insulin requirement affected the variation of total cholesterol in women with GDM. The development of GDM may be a predict factor of possible future cardiovascular or metabolic disease. The control of the lipid profile after gestational diabetes mellitus can be an interesting opportunity to screen women with dyslipidemia and to institute effective management strategies to reduce this cardiovascular risk factor.

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P312

Secondary diabetes associated with principal endocrinopathies (about 161 cases)

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Background
Many endocrine diseases can be complicated by diabetes, due to hyperglycemic hormones and insulinresistance. The aim of the work was to analyze prevalence, therapeutic and progressive aspects of secondary diabetes as well as carbohydrate intolerance (CHI) in patients with an endocrinopathy.
Materials and methods
A retrospective study was conducted in the endocrinology and diabetology department including 161 patients followed for diabetes or CHI and endocrinopathy (hyperthyroidism, acromegaly, pheochromocytoma and hypercorticism) between 2005 and 2017 among all endocrinopathies (365 cases). Variables studied in these patients were imbalance degree, degenerative complications, treatment and evolution.
Results
Mean age was 33.5(18-71) years with a female predominance. The etiologies were represented by hypercorticismin 57 patients, acromegaly in 38 patients, pheochromocytoma in 27 patients and hyperthyroidism in 39 patients. General diabetes prevalence was 44%. Concerning etiology, diabete prevalence of acromegaly was 34%, for hypercorticism (63%), for hyperthyroidism (33.3%) and for pheochromocytoma (38%).The prevalence of IHC was 18,6%. Diabetes revealed the endocrinopathy in 30 patients. The mean HbA1c was 9.3%. The degenerative assessment had objectified a diabetic retinopathy (16%), a nephropathy (12%), a neuropathy (7%) and hypertension (50%). Therapeutic management consisted of treatment with ADO (32%) and insulintherapy (52%). Among the patients treated and cured of their endocrinopathy (69%) we noted a diabetes regression in 78% of cases and diabetes persistence with therapeutic needs regression in 22% of cases.
Conclusion
The prevalence of secondary diabetes varies according to endocrinopathy. It can reveal the disease and associated with other metabolic disorders. Adequate screening and management is recommended in the presence of endocrinopathy.

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P313

Metabolic syndrome and triglyceride-rich lipoproteins

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Introduction
Hypertriglyceridemia, a cardinal feature of metabolic syndrome (MS), is associated with cardiovascular disease and abnormal metabolism of apolipoproteins which may form the basis for this relationship. The aim of this study is to evaluate triglyceride-rich lipoproteins profile in MS patients.
Material and methods
A retrospective study was performed, including patients evaluated in a tertiary hospital. Patients with thyroid dysfunction, neoplastic disease, HIV, severe hepatic or renal disease, genetic dyslipidemia or under treatment with corticosteroids, fibrates or ezetimibe were excluded. MS was classified using the American Heart Association/National Heart, Lung and Blood Institute definition.
Results
We included 75 patients with MS, mean age 55.05 ± 11.5 years, body mass index (BMI) 29.72 ± 4.5 kg/m^2, waist circumference (WC) 102.28 ± 10.8 cm, 44% female and 72 patients without MS, mean age 42.74 ± 16.3 years, BMI 25.81 ± 4.5 kg/m^2, WC 92.24 ± 14.7 cm, 59.7% female. Patients with MS presented significantly elevated levels of triglycerides (200.68 ± 129.5 vs 98.14 ± 46.6 $P<0.001$) and ApoCII (7.80 ± 4.3 vs 4.88 ± 4.2 $P=0.006$) and lower levels of ApoA1 (140.80 ± 27.6 vs 165.50 ± 35.1 $P<0.001$). Only 16.7% of MS patients had ApoCIII levels within normal range, the remaining 83.3% presented elevated levels whereas in patients without MS, only 46.2% had elevated ApoCIII levels ($X^2=0.001$). We found no correlation between ApoCII, ApoCIII or ApoA1 and age, BMI, WC or blood pressure.
Conclusion
Increased apoC-II and ApoCIII and decreased ApoA1 levels are common in the MS phenotype. ApoCIII is thought to have a direct role in atherogenesis, and their elevated levels in MS patients may further aggravate their cardiovascular risk. Understanding ApoC lipoproteins metabolism can contribute to develop new therapeutic targets for MS.

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P314

Specificity of mathematical indexes versus histopathological findings in the diagnosis of nonalcoholic fatty liver disease in mexican population

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is an emerging disease in Mexico and it could become in a public health problem, this one understands a spectrum of

histopathological findings ranging from simple steatosis to steatohepatitis and cirrhosis. The gold standard continues to be the liver biopsy, but several mathematical indexes have been proposed, such as non-invasive techniques, however there are very few studies in our population. This study aims to compare the specificity of mathematical indexes and histopathological findings for the detection of NAFLD in Mexican population.
Methods
A cross-sectional study was performed at the 'Hospital General Regional de León'. Patients aged 18 years or above that underwent laparoscopic cholecystectomy were recruited. No history of alcohol consumption habit or hepatic diseases characterized the patients. The fatty liver index (FLI) and the lipid accumulation product (LAP) were calculated. Demographics, blood samples, and a liver biopsy were obtained. Results between FLI, LAP and livery biopsy were compared. The area under de curve (AUC) was calculated for each mathematical index SPSS V21 was used for statistics analysis.
Results
A total of 152 patients were included (84.9% women and 15.1% men). The mean age was 38.7±12 years, BMI 28.8±5.3 kg/m^2. The FLI identified 80 patients with NAFLD of whom 60% were corroborated with biopsy, whereas the LAP identified 87 patients of whom 55.2% were corroborated with biopsy. From the patients with FLI negative index (n=72), a total of 26% has a histopathological diagnosis of steatosis. For LAP, 65 patients were negative, of which 29.2% presented positive biopsy for the presence of NAFLD. The AUC for FLI was 0.69 whereas the AUC for was LAP 0.68 using ROC curve.
Conclusion
According to our results, the efficiency of these two mathematical indexes are regular for the diagnosis of NAFLD due their specificity at least our population, so liver biopsy remains to be the gold standard for the detection of NAFLD in our population. Future studies should be performed in order to continue looking for other non-invasive markers for NAFLD.

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P315

What changes does pregnancy bring to the lipid parameters of diabetic patients?

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Objective
The objective of our study is to describe the lipid parameters of pregnant women with diabetes during the three trimesters of pregnancy.
Materials and methods
This is a retrospective study that looked at 44 diabetic pregnant women. Clinical biological data were collected from medical records. The personal history of dyslipidemia, pathologies, and medications that may interfere with lipid parameters have been eliminated.
Results
Patients in the first trimester of pregnancy had a mean age of 33.5 years +/−6.3 (33.4+/−5.8 in T2 and 33.1+/−5.5 in T3). Diabetes was type 1 in almost 100% of cases (it was type 2 in 62.5% of patients in T2 and in 60% of patients in T3). The average pre-perceptible body mass index was 27.4 kg / m2+/−4.5 (29.2 kg / m^2+/−5 in T2 and 28 kg / m^2+/−3.3 in T3). on average 10.7 years +/−2.1 (7.2 years +/−5.4 in T2 and 6.6 years +/−4.6 in Q3) with an average HbA1C of 9.1%+/−1, 1 (7.9%+/−0.3 in T2 and 8.1%+/−0.4 in T3). The average triglyceride level was 1.1 mmol / L+/−0.3 (1.6 mmol / L+/−0.5 in T2 and 1.7 mmol / L+/−0.4 in T3). Mean cholesterolemia was 4.5 mmol / L+/−0.7 (4.9 mmol / L+/−0.7 in T2 and 5.2 mmol / L+/−0.6 in T3). Hypercholesterolemia was noted in only one patient (18.7% in T2 and 60% in T3). Hypertriglyceridemia was also noted in one patient (in 50% of patients in T2 and in 60% of patients in T3). All patients had normal HDL-CT regardless of the trimester of pregnancy. All patients, except two in T1, were outside the LDL-CT goal, which averaged 1.03g / L+/−0.2, in T1, 1.05g / L+/−0.2 in T2 and 1.1g / L+/−0.2 in T3.
Conclusion
In our population, it has been noted that hypercholesterolemia and hypertriglyceridemia are lipid abnormalities whose frequency increases with the evolution of pregnancy. A larger sample of diabetic patients is needed to better characterize changes in lipid parameters during pregnancy.

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P316

Identifying metabolic unhealthy obesity using the product of triglycerides and glucose

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Introduction
There are significant physiologically and clinically differences in profiles between metabolic healthy and metabolic unhealthy obese individuals. Several markers are on study in order to better characterize the metabolic profile of metabolic unhealthy obese individuals. The aim of this work was to determine whether the triglycerides/glucose (TyG) index may be a valuable marker for identifying metabolically unhealthy obesity.
Methodology
Metabolic unhealthy obesity was defined as the presence of ≥3 of the following: blood pressure ≥130 and/or ≥85 mmHg or anti-hypertensive drug use; triglycerides ≥150 mg/dL or anti-dyslipidemic drug use; high-density-lipoprotein <40 mg/dL in males and <50mg/dL in females; fasting glucose ≥110 mg/dL or anti-diabetic drug use and waist circumference (WC) ≥102 cm in males and ≥88 cm in females. The TyG index was calculated as ln[fasting triglycerides (mg/dl) x fasting glucose (mg/dl)/2].
Results
We included 84 individuals, mean age 53.3±12.4 years, mean body mass index (BMI) 33.55±3.4 kg/m^2, mean WC 108.6±8.7 cm, 50% female. 88.1% (n=74) were classified as metabolic unhealthy obese individuals. These patients presented a superior TyG index compared to patients with metabolic healthy obesity (9.38±0.7 vs 8.54±0.7 P=0.001). Patients with metabolic unhealthy obesity also presented a significant larger WC and significantly low levels of HDL cholesterol and elevate levels of oxidized LDL-cholesterol. We did not find differences in respect to LDL cholesterol, uric acid and ultra-sensitive-PCR between the two groups of patients. ROC curves evidenced that a cut-off point of TyG index >8.94 identifies patients with a greater probability of having a metabolic unhealthy obesity (Sensitivity: 71.9%; Specificity 80.0%; AUC 0.822; P< 0.001).
Conclusion
We found that individuals with metabolic unhealthy obesity presented a higher TyG index compared to those with metabolic healthy obesity and that this index has a good specificity and sensitivity in identifying this type of obese individuals. Larger studies are necessary to validate this marker in our clinical practice, nevertheless, these data highlight the value of the TyG index in discriminating those obese subjects with metabolic dysregulation.

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Clinical case reports – Thyroid/Others

P317

Diabetic ketoacidosis occurring in the patient whom newly started insulin glargine U300: a case report

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Basal insulin secretion is essential for the maintenance of fasting glucose levels, especially through inhibition of excessive hepatic glucose output. Insulin glargine U300 is a novel long acting basal insulin formulation that provides more stable effect than glargine U100. Because of the pharmacokinetic properties of glargine U300, the expected plasma insulin concentration is not achieved during the first 4 days of treatment. We report a case of diabetic ketoacidosis in the first day of glargine U300 treatment due to low plasma insulin concentration. A 62 year old female patient with diagnosis of type 2 diabetes mellitus (DM) for 25 years. Her medications include insulin aspart 12 unit three times daily, insulin detemir 22 unit once daily, metformin 1000 mg twice daily, linagliptin 5 mg. According to the patient's anamnesis, it has been noticed that in addition to the especially night hypoglycemia, the blood glucose levels of fasting and postprandial in the evening were high and she said that did not adhere to her diet. Physical examination revealed that her BMI is 33 kg/m^2. Laboratory findings were as follows; HbA1c: 10.3%, c-peptide: 0.07 µg/L, Hb: 9.2 g/L, MCV: 89 fL, ferritin: 7.93 µg/L. The patient was hospitalized to regulate her blood glucose and to investigate anemia etiology. Insulin detemir, used by the patient were replaced by insulin glargine U300 U/mL, 30 units once daily because of the hypoglycemia at night and the high blood sugar levels in the evening. On the second day of treatment, abdominal

ultrasound examination is demanded from the patient to research anemia etiology in the morning and as fasting. Blood glucose was measured 450 mg/dL after returning from the ultrasound when she had not eaten breakfast. It was detected that the ketone in the urine and pH: 7.29, hCO3: 14 mmol/L in the blood gas of the patient with complaints of nausea and fatigue. Insulin infusion was initiated by considering mild diabetic ketoacidosis in the patient. For treatment of insulin glargine U300 U/mL to be stable, 4 days must pass. For the first 4 days, it may be seen the diabetic ketoacidosis on the patients who have type 1 DM and, as in this case, long-term type 2 DM with decreased insulin reserve, that are treated with newly started insulin glargine U300 due to inadequate plasma basal insulin.

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P318

A female patient with diabetic ketoacidosis who had hyperthyroidism and acute appendicitis

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Introduction
Hyperthyroidism is defined as thyroid hyperfunction due to overproduction of thyroid hormones. Graves disease is the most common cause of hyperthyroidism. Hyperthyroidism may be associated with glycemic dysregulation. We are presenting a case with diabetic ketoacidosis who had Graves disease and acute appendicitis.
Case presentation
A nineteen years old female patient wtih Graves disease who had hyperthyroidism despite high dose antithyroid medication. She applied with diabetic ketoacidosis and acut appendicitis. Respiratory arrest developed and she was intubated. Hydration, electrolyte replacement, HCO3 replacement and intravenous insulin started due to diabetic ketoacidosis. Surgical treatment was planned for acut appendicitis. Potassium iodide, anti- thyroid theraphy and beta-blocker was started. Appendectomy was performed under spinal anesthesia after diabetic ketoacidosis had partially improved. Post-operative propylthiouracil 20tb / day, beta-blocker and cholestyramine treatment was given. Free thyroid hormones were normal after these treatment and total thyroidectomy was planned.
Conclusion
Hyperthyroid patients have an higher risk to develop hyperglycemia. Possible mechanisms are increased hepatic glucose output, rapid glucose absorption from the intestine, increased gluconeogenesis and insulin resistance. Patients presenting with diabetic ketoacidosis should be carefully evaluated in terms of precipitating factors such as hyperthyroidism.

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P319

Factitious hypoglycemia; Case report

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Introduction
Hypoglycemia is defined as a reduction in plasma glucose concentration to a level that may induce symptoms such as sweating, shaking, palpitation, headache, *blurry vision*, loss of consciousness, *seizure*, *coma*. We present a case with hypoglycemia which is due to the use of exogenous insulin.
Case presentation
A 72-years-old patient with Alzheimer disease who was admitted to the emergency clinic because of unconsciousness.Plasma glucose was 25 mg/dl at this time and concurrently measured insulin and C-peptide value were >1000 uU/ml and 0.31 ng/ml, respectively.The patient's plasma glucose was increased and consciousness was improved by intravenous dextrose. Injection areas were observed in the skin of the abdomen on physical examination.Present findings supported hypoglycemia which was associated with the use of exogenous insülin. However, patient's relatives denied the use of exogenous insülin.Insulin antibody was screened to exclude autoimmune hypoglycemia. Insulin antibody was not detected. The patient was followed up, insulin and C-peptide levels returned to normal 10 days later (insulin 11.22 and C-peptide 4.41 ng/ml)
Conclusion
Exogenous administration of insulin results an increase on insulin levels without a concomitant increase in the C-peptide level.Factitious hypoglycemia should be kept in mind especially in elderly patients in need of care for others.

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P320

Development of fatal lactic acidosis after inadvertent use of metformin in a non-diabetic hemodialysis patient

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Metformin is considered to be the first choice in the treatment of type 2 diabetes mellitus. Lactic acidosis is a rare life-threatening complication of metformin with approximately 50% overall mortality. Metformin is contraindicated in patients with factors predisposing to lactic acidosis such as impaired renal function (eGFR <30 mL/min). Herein, we present a hemodialysis patient who developed lactic acidosis after inadvertent usage of metformin.
Case report
A 77-year-old woman was admitted to the emergency department with complaints of nausea, vomiting, black stools, weakness and deterioration in general condition. The patient underwent regular hemodialysis twice a week for 1.5 years due to hypertension and end-stage kidney disease. She was anuric for one year. The last dialysis session was performed 3 days ago. Her family said she had inadvertently received six metformin tablets resembling calcium acetate pills, three in the morning and three in the evening, two days ago. Metformin belonged to one of the family members. She was afebrile, tachypneic, agitated and confused. Heart rate was 145 b/min, blood pressure 70/30 mmHg and oxygen saturation in the room air 75%. There was no significant cardiovascular and pulmonary findings. Laboratory tests showed glucose 88 mg/dl, urea 199 mg/dl, creatinine 10.1 mg/dl, sodium 134 mmol/l, potassium 6.3 mmol/l, white blood cell 42.7 K/mm^3 and hemoglobin 10.5 g/dL. Her liver function tests were normal. Wide-anion gap metabolic acidosis without ketonemia was detected. The pH was 6.9, bicarbonate (HCO_3^-) 6 mmol/L, and lactate 140 mmol/L. Metformin-induced lactic acidosis was diagnosed. She was treated with positive inotropic support and bicarbonate infusion. Hemodialysis with bicarbonate buffered replacement fluid was started to remove metformin and correct lactic acidosis. After dialysis, control blood gas values were mildly improved (pH 7.16, lactate 108 mg/dL and HCO_3^- 13.8 mmol/L). Then, despite the dialysis treatment, acidosis deepened (pH 6.8, HCO_3^- 6 mmol/L and lactate 170 mg/dL) and she died with sudden cardiac arrest.
Conclusion
Lactic acidosis and/or hypoglycemia have been reported after inadvertent metformin overdose in diabetic hemodialysis patients. Our case was the first non-diabetic patient who developed lactic acidosis after accidentally metformin use. Significant lactic acidosis occurs only in the presence of comorbid conditions including kidney failure. Drug use should be controlled in elderly dialysis patients.

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P321

Effect of hemoglobin J variant on HbA1c values as measured by HPLC (high-perfomance liquid chromatography)

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Hemoglobin A1c (HbA1c) is used for the long-term management of patients with diabetes mellitus (DM). Hemoglobin variants other than HbA1c and e-N-lysine-glycated HbA0 may cause analytical interference in determinations of HbA1c.

Hemoglobin J is an abnormal hemoglobin, an alpha globin gene variant and present in various geographic locations. Hemoglobin J (depending on its type) has different characteristics and functions. For example hemoglobin J Capetown (α2 92Gln β2), the most commonly seen Hb J variant (CGG->CAG), is associated in the heterozygous state with increased oxygen affinity and polycythemia. Other variants like Hb J Sardegna will show a completely unremarkable clinical picture in the heterozygote. Hemoglobin J Bancock (beta 56 Gly->Asp) and J Baltimore (beta 16 Gly->Asp) have been described in combination with sickle hemoglobin. Recently, Valencia Clinical Hospital discovered a new variant named Hemoglobin J Valencia; it was discovered after routine glycemic testing was carried out on a person with Diabetes, with the results of the test coming back abnormally low within the parameters. We describe the case of a 39-year-old caucasian male with history of HIV who presented to our institution for elevated HbA1c, with normal fasting glycemia. He was first diagnosed with HIV two years ago, when infectious disease specialist determined HbA1c for the first time (as a protocol), obtaining 12%. Our patient was also receiving treatment with Efavirenz, Tenofovir and Emtricitabine (HIV therapy). Fasting glycemias were always normal, so the doctor recommended metformin 850 mg twice daily. No hemoglobinopathy was known or suspected, as the blood count was normal; {red blood cells =5.89 million/mm^3 [reference interval (RI) =4.5-6 million/mm^3}; hemoglobin =17.2 g/dl (RI =13-18 g/dl); hematocrit =51.4% (RI =40%-55%). Previous values of HbA1c were: 12.0% (29/04/2015), 11.5% (27/01/2016) and 11.8% (28/06/2016); and fasting plasma glucose concentrations were 89 mg/dL, 96 mg/dL and 93 mg/dL, respectively. As these results did not correlate between them, we gave him a continuous glucose monitoring system; he worn it for one week. Time in target was 95%; glucose trend, 93 mg/dL, and no low glucose event was detected. Taking all these data into account, we performed a test for identification of hemoglobin variants using HPLC, which presented: HbA0=56.2%; HbA2=3.3%; and the presence of probable HbJ =39.2%. As a result, real HbA1c was lower than we could first determine.

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P322

Performance-enhancing drugs and adverse endocrine effects

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Introduction
Performance-enhancing drug (PED) use is currently a common practice both inside and outside the sports competition scenario, and its adverse health effects remain underappreciated.
Case report
We report the case of a 26-year-old man, bodybuilding practitioner, no relevant medical history, family history of autoimmune disorders. Referred to the emergency room with polydipsia, polyuria, blurred vision associated with a post-prandial capillary blood glucose of 422 mg/dl. Initial testing revealed glucose 281 mg/dl, normal liver tests and renal function, no acidosis, no significant ketonemia. He had participated in a bodybuilding competition four days before and used the following PED (6 weeks cycle before the competition): androgenic-anabolic steroids – testosterone cypionate 500 mg/wk, trenbolone 100 mg every other day, stanozolol 40 mg id, boldenone 1200 mg/wk, sustanon® 250 mg twice weekly, testosterone enanthate 250 mg id, drostanolone propionate 100 mg every other day, mesterolone 25 mg 4-6id, fluoxymesterone 75 mg id; dopaminergic agonist – cabergoline 0.25 mg every other day; aromatase inhibitor – anastrozole 1 mg id; beta 2-adrenergic receptor agonist – clenbuterol tid; thyroid hormones – levothyroxine 100 mcg id, liothyronine 25 mcg bid; non-specified multivitamins. On the day of the competition, he took diuretics (altizide + spironolactone). He had done similar cycles since he was 21 years old. Hospitalized for suspected diabetes Mellitus (DM). Body mass index 21.1 kg/m^2, with fat mass 2.7 kg (5.5–13.7) and lean mass 61.8 kg (52–60.2). He maintained blood glucose 70–130 mg/dl. Hematocrit was increased (53%). A posterior analytic evaluation revealed oral glucose tolerance test with impaired glucose tolerance, positive diabetes autoimmunity, A1c 5.8%, C peptide 1.7 ng/ml (1.0–7.6). Autoimmune thyroiditis was also detected, with mild subclinical hypothyroidism. Pituitary function assessment showed hypogonadotropic hypogonadism (total testosterone 0.9 ng/dl), without evident signs or symptoms. He maintains irregular follow-up.
Discussion
A wide range of endocrine adverse effects of PED use are described. Altered glucose homeostasis can occur through increasing insulin resistance, which can accelerate DM natural history in individuals with positive autoimmunity. Anabolic steroid-induced hypogonadism is caused mainly by feedback suppression of the hypothalamic-pituitary-gonadal axis and can be irreversible, leading to infertility. Although complications related to PED use are known, there is scant scientific evidence regarding the long-term consequences and complex endocrine disruption likely caused by the stacking and cycling of multiple high-dose synthetic androgens and other classes of PED. Clinical and hormonal function evaluation of these athletes is difficult, as they are using unregulated or non-authorized drugs and can have a low level of trust in the medical community.

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P323

Maturity – onset diabetes in the young and non-alcoholic fatty liver disease: a case report

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Introduction
Maturity-onset diabetes of the young (MODY) is a form of diabetes mellitus transmitted by an autosomal dominant mode of inheritance, usually diagnosed before the age of 25 years. Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease, particularly closely related with insulin resistance and type 2 diabetes mellitus. MODY and NAFLD combination has rarely been described in the literature.
Case
A 25-year-old women was admitted to the Hospital of Lithuanian University of Health Sciences, Kauno klinikos to verify diabetes type. She has been diagnosed with type 1 diabetes a year ago. Despite dietary control and a basal-bolus insulin therapy, her glycaemic control was inadequate with glycosylated haemoglobin (HbA1c) 8.8%. Blood tests for islet-cell antibodies and glutamic acid decarboxylase autoantibodies were negative (anti GAD65 0.25 IU/ml (normal range 0–1), anti IA2 0.05 U/ml (0–1), anti-insulin 4.5% (<6.4), with enough insulin secretion (C-peptide before eating 1.49 nmol/l (0.36–1.09)). A missense GCK gene mutations were confirmed by genetic (NM_000162.3(GCK):c.[679+38T>C]); [679+38T>C]), suggesting diagnosis of MODY 2 diabetes. The insulin therapy was gradually withdrawn and sulfonylurea was introduced. Patient had no history or risk factors of liver disease, with body mass index (BMI) 27.6 kg/m^2 and minor dyslipidaemia. Her liver function tests showed moderate elevations of liver enzymes (aspartate aminotransferase (AST) 147 U/l (0–35), alanine aminotransferase (ALT) 143 U/l (0–45), γ-glutamyl transferase (GGT) 168 U/l (0–55)), with normal bilirubin's levels. Serum hepatitis markers, autoantibody screenings were negative, ceruloplasmin was normal (0.36 g/l (0.22–0.58)). There was a moderate increase in ferritin (354.4 μg/l (20–275)) with normal saturation (34% (15–45)). A liver ultrasound showed increased echogenicity with diffuse fatty infiltration confirming diagnosis of NAFLD. Despite 3 months of treatment by 280 mg silymarin and statins, her liver enzymes remained elevated. Finally, insulin therapy was resumed, because with dietary control and 120 mg of gliclazide, glycaemic control persisted to be inadequate. After 6 months, liver enzymes decreased and glycaemic control improved.
Conclusions
Coexistence of MODY and NAFLD is rare and it is hard to distinguish a causative relationship. Therefore, research and new management strategies for this pathology are urgently needed.

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P324

Dapagliflozin and Atkins Diet in a patient with type 2 Diabetes Mellitus: A combination that should be avoided

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Introduction
Prevalence of type 2 diabetes mellitus (T2DM) rises rapidly worldwide and most patients with T2DM are obese. All treatment algorithms advocate lifestyle modification and weight loss in combination with various therapeutic categories available for the treatment of T2DM, resulting in diet-antidiabetic drug combinations that are not always proper or safe for the patients.
Case presentation
A 73-year-old Caucasian man presented to the emergency department of our hospital with weakness and malaise gradually deteriorating over the previous 3 days, accompanied by anorexia, nausea and vomit tendency over the last 24 hours. He had a previous history of hypertension, diagnosed 15 years ago, currently treated with felodipine and metoprolol. He also had a history of T2DM diagnosed 10 years ago, currently treated with metformin, sitagliptin and dapagliflozin. Despite his poor general condition and his reduced food intake he continued all his medications. The patient was obese, struggling with several weight loss efforts over the last ten years. The week before admission to the hospital he had started an Atkins diet. Physical examination at the time of admission revealed signs of dehydration. Patient vitals were within normal range. His point-of-care blood glucose value was 143 mg/dl. He had moderate tenderness to palpation in the upper abdomen, while the remainder of the clinical examination was normal. On admission serum creatinine and uric acid were increased while the rest of the biochemical tests were normal. Estimated serum osmolality was 308 mOsm/kg. His arterial blood gas showed a pH 7.19, PCO2 of 34 mmHg, PO2 of 103 mmHg, bicarbonate of 13.5 mmol/l and an anion gap of 24 mEq/l. He had increased blood β-hydroxybutyric acid and urine ketones in the urine analysis. The diagnosis of euglycemic diabetic ketoacidosis (euDKA) was established and he was treated with intravenous fluids, glucose and insulin.
Conclusions
Sodium-glucose cotransporter-2 (SGLT2) inhibitors lower plasma glucose and favour weight loss by promoting glycosuria and inhibiting glucose reabsorption. Low carbohydrate diets force the body into ketogenesis, causing a state of relative metabolic acidosis even in non-diabetic patients. This case indicates that these diets should be avoided in T2DM patients on SGLT2 inhibitor treatment, since both SGLT2 inhibitors and low carbohydrate diets (such as Atkins diet) can induce ketogenesis or even ketoacidosis in the presence of a triggering factor, reflecting a life-threatening ketogenic combination.

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A rare cause of hypoglycemia: insulin autoimmune syndrome in a Turkish patient taking Alpha lipoic acid

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Insulin autoimmune syndrome (IAS) is a rare cause of hypoglycemia and characterized with autoantibodies to insulin in a patient without prior exposure to exogenous insulin. Medications with sulfydryl group and autoimmune diseases are known to be associated with this syndrome. Nearly 90% of the cases were reported in Japanese patients. We presented a Turkish patient with insülin autoimmune syndrome possibly caused by α-lipoic acid. A 62-year-old woman was admitted to our clinic recurrent episodes of sweating, weariness, heart palpitations and anxiety occurring both fasting and postprandial. The first episode was two weeks before admission and the capillary glucose was measured as 40 mg/dl during episode. She had been diagnosed with hypertension and hyperlipidemia for ten years and treated with indapamid, nebivolol and atorvastatin. She had never been diagnosed as diabetes mellitus and never injected insulin before. She had no family history of diabetes or autoimmune disease. She had been taken multivitamin preparation which contained α-lipoic acid until three weeks prior to her hospitalization. Laboratory investigations revealed normal renal and liver functions. During hypoglycemic event, serum glucose was 46 mg/dl; serum insulin was 1890 μIU/ml (normal: 1.9-23) and C-peptide was 11.9 ng/mL (normal value 0.9–7.1). Proinsulin levels was 33.8 pmol/l (normal: <8). An oral glucose tolerance test showed hypoglycemia with inappropriately high insulin levels at 300 min. The 72-h fasting test, abdominal computed tomography (CT) and magnetic resonance imaging (MRI) were normal. Insulin recovery was 6.6% after polyethylene glycol precipitation. No interference was detected with heterophile blocking tubes. Insulin antibodies was measured as 79% (normal: <8.2) and the patient was diagnosed as insulin autoimmune syndrome. Patient was instructed not to use the suspected medication again. Diet with low carbonhydrate and frequent small meals was planned. Her symptoms resolved and no hypoglycemic event was recorded. Insulin levels have decreased from 1890 μIU/ml to 76 μIU/ml (normal: 1.9-23) during follow-up. In all hyperinsulinemic hypoglycemic cases, especially in patients taking medications known to be associated with the syndrome and having very high insulin levels, the diagnosis of insülin autoimmun syndrome should be kept in mind.

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Post bariatric surgery malabsorption and vitamin D deficiency

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Introduction
Bariatric surgery is a revolutionary method for the treatment of morbid obesity. It is effective as far as weight control is concerned, for the prevention and treatment of diabetes mellitus and the metabolic syndrome. However, bariatric surgery may be accompanied by adverse effects if postoperatively dietary instructions are not adhered to.
Aim
The aim was to present a case of a patient who underwent sleeve gastrectomy for the treatment of morbid obesity and postoperatively developed severe malabsorption and vitamin D deficiency.
Methods
The case of a patient, female, aged 50 is described, who suffered from morbid obesity, body weight being 250 kg, BMI 91.83. The patient underwent sleeve gastrectomy, the treatment being effective as far as weight loss is concerned, as she lost weight. However, in the course of the disease the patient did not comply with dietary instructions. She developed diarrhea, severe malabsorption, severe vitamin D deficiency and spontaneous rib fractures. Additionally, she developed hidradenitis suppurativa.
Results
An intestinal biopsy was performed which showed non-specific intestinal inflammation. However, the syndrome of diarrhea was so severe, that mesalazine was administered. Mesalazine administration improved diarrhea. A month ago, the patient presented with generalized bone and muscle pain, cardiac insufficiency and respiratory insufficiency. Plasma $25(OH)D_3$ was 3 ng/ml (normal range >30 ng/ml), PTH 280 pg/ml (normal range 10–65 pg/ml) and plasma calcium 8.4 mg/dl. Cholecalciferol was administered in high dosage and generalized pain improved.
Conclusions
Morbid obesity may be a manifestation of severe depression, which affects dietary behavior and may manifest as bulimia. Surgical treatment of obesity improves body weight however it does not improve depression. Dietary behavior may persist with destructive effects on the gastrointestinal system and the organism, such as premature ageing, diarrhea and malabsorption with vitamin and micronutrient deficiency. In particular vitamin D deficiency may induce osteomalacia and generalized bone and muscle pain. In the case described, the patient developed hidradenitis suppurativa, which, being an autoimmune disorder, may have been partially induced by vitamin D deficiency.

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P327

Diabetes and bulimia – a dangerous combination

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Introduction
Bulimia is an eating disorder characterized by constant preoccupation with food, irresistible cravings for food and binge eating episodes. The data regarding the incidence of bulimia in people with diabetes are contradictory. The glycemic variations subsequent to binging and vomiting leads to complications like retinopathy, kidney or liver failure, hypoglycemic comas and electrolyte imbalances.
Case presentation
A 57-year-old female, diagnosed with type 2 diabetes at the age of 33, complicated by diabetic polyneuropathy and under treatment with Metformin (2 g/day), glargine (96 IU/day) and glulisine (32 IU/day) was admitted to our center for persistent hyperglycemia (Gl max = 430 mg/dl), polyuria, polydipsia, nocturnal enuresis, xerostomia and nocturnal paresthesia in the upper and lower limbs. Despite her associated disorders (recurrent depression and bulimia) untreated properly, she underwent a gastric plication procedure with an initial weight loss of 20 kg regained after a period of 2 years. At admission: depressive facial affect, BMI = 42.87 kg/m^2, distended abdomen due to fat tissue with multiple surgical scars, psoriatic lesion on the posterior thorax, elbows and lower limbs and acanthosis nigricans on the neck. Labs exams revealed: Gl = 304 mg/dl, hypertriglyceridemia, low calcium and magnesium levels, glycosuria and poor glycemic control in the last 3 months (A1c = 11.4%). The 24-hour weighed food diary showed a caloric intake higher than her daily requirements with 3 main meals and 4 snacks (consisting of fruits, sweets, bread and yogurt). To improve the glycemic and weight control the prandial insulin was stopped and Exenatide 10 μg bid was initiated, alongside with a low caloric diet of 1200 Kcal/day and resumed therapeutic education with a favorable outcome. The psychological and psychiatric consults confirmed the previous diagnoses and recommended increasing the Fluoxetine to 40 mg/day, monthly reevaluation and cognitive behavioral therapy. The hormonal profile excluded other secondary causes of obesity. The neuropathic symptoms diminished significantly under i.v treatment with α-lipoic acid. The Doppler exam displayed decreased values of the ankle-brachial index.
Conclusions
The data regarding the incidence of bulimia in people with diabetes are contradictory and the factors which may underlie the link between diabetes and bulimia have not been systematically investigated. The screening for bulimia and other eating disorders may be an efficient tool for detection and implementation of the multidisciplinary approach in order to obtain the therapeutic success.

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Prolonged hyperglycemia in a type 1 diabetic futsal player after a single betamethasone injection for pain in the groin area

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Introduction
Pain in the groin area is frequently encountered in football players, the cause being a sport hernia, muscle tears, avulsions, sacroiliac joint pathology, etc. Local corticosteroid injections (LCIs) are often used as one of the first-line treatments in the conservative management because of their ease of delivery, low cost and efficacy.
Case presentation
A 32-year-old amateur futsal player (goalkeeper) diagnosed with type 1 diabetes at the age of 18, complicated by mild peripheral polyneuropathy, treated with aspart insulin through an insulin pump (basal rate = 25.7 IU/day and boluses = 35 IU/day) was admitted to the Clinical Recovery Hospital for an intense pain in the left groin area (9/10 on VAS), located profound and aggravated by any physical activity. The patient was previously treated with Celecoxib 90 mg/day in 2 cycles of 7 days at one month's interval. At admission: BMI = 26 kg/m^2, BP = 120/80 mmHg, Pulse = 70/min, flat feet, bilateral hallux valgus, cracking sounds on knees mobilization, lipohypertrophy due to insulin therapy under umbilical area. Labs exams revealed: Gl = 173 mg/dl, A_1c = 6.7% and negative inflammatory markers. The X-rays displayed an avulsion of the antero-inferior iliac spine (AIIS) confirmed by CT scan which also revealed the preservation of the muscle tendon insertion and a partial tear of the left rectus femoris. Under treatment with Celecoxib (30 mg/day), Tramadol + Acetaminophen 37.5/325 mg (bid) and local Ketoprofenum 2.5% applications the pain intensity decreased slightly (6/10 on VAS). In order to optimize the pain management a Betamethasone injection 1 ml (7 mg) in the groin area was administered in the 4th day of hospitalization. In order to maintain an optimal glycemic control significant increases of both basal rate (120% - 140% - 160%) and prandial boluses (with 2, 4 and 5 IU) were necessary. The highest glycemic value was 456 mg/dl and was documented in the 4th day after LCI. The patient returned to his initial insulin doses in the 9th day after LCI. The improvement in pain symptoms lasted for almost 6 months.
Conclusions
This case report demonstrated that a single injection of Betamethasone can cause a significant rise in the average daily insulin requirements needed to control blood glucose levels. The medical practitioners should warn type 1 diabetic patients about this possible side effect and must advise a more frequent monitoring in order to detect and correct the hyperglycemic events.

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Developmental endocrinology

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Glucose, lipids, and insulin in cord blood of neonates and their association with birth weight

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Background
Low and high birth weight (BW) has been linked to the increased risk of infant mortality, obesity, diabetes, and cardiovascular diseases. Metabolic biomarkers, glucose, lipids and insulin in human umbilical cord blood could potentially reflect the new-born metabolic status. This study aims to assess the concentration of glucose, lipids and insulin in cord blood, and to investigate the association between these metabolic parameters and BW.
Methods
A total number of 1522 mother-baby pairs from the Born in Guangzhou Cohort Study (delivered during January 2015–June 2016) were included into this analysis. Data on cord maternal gestational metabolic characteristics, delivery information, cord blood metabolic parameters (glucose, lipids and insulin concentrations) and BW were prospectively collected. Associations between cord blood metabolic parameter z-scores and BW z-score were assessed using multivariable linear regression, adjusted for maternal age, gestational age, parity, gender, delivery mode, maternal metabolic characteristics (2nd trimester glycaemic status and triglycerides level) and sample storage duration.
Results
Other than insulin (median[IQR]: 7.43[4.34, 12.61]) μU/ml) and triglycerides (TG, median[IQR]: 0.33[0.27, 0.41] mmol/l), the concentrate distribution of glucose, total cholesterol (TC, mean ± s.d.: 1.72 ± 0.42 mmol/l), high-density lipoprotein cholesterol (HDL, mean ± s.d.: 0.91 ± 0.28 mmol/l), low-density lipoprotein cholesterol (LDL, mean ± s.d.: 0.61 ± 0.24 mmol/l) in the cord blood were normal distributed. Z-score of glucose concentration in the cord blood was not associated with BW ($P = 0.81$) z-score. Z-score of cord blood TC (β[95%CI]: 0.05[0.01, 0.09]), HDL (β[95%CI]: 0.08[0.04, 0.12]), and insulin (β[95%CI]: 0.21[0.17, 0.25]) were positively associated with BW z-score, while TG z-score was inversely associated with BW z-score (β[95%CI]: −0.22[−0.27, −0.18]).
Conclusion
Our findings suggest new-borns with higher BW centile might have increased risk of insulin insensitivity and high TG consumption rate. Insulin and TG concentrations in cord blood potentially reflect new-born metabolic status.

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Association of RS1170806 polymorphism in *ADCY5* and RS7754840 polymorphism in *CDKAL1* with birth weight, neonatal glucose, insulin and insulin resistance.

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Background
The fetal insulin hypothesis proposes that low birth weight, insulin resistance, and decreased insulin secretion in adulthood are genetically mediated. Babies with low birth weight have higher morbidity and mortality risk in adulthood. However, this situation could also occur in children with adequate weight at birth with genetic risk factors. The polymorphisms rs11708067 in *ADCY5* and rs7754840 in *CDKAL1* have been associated with low birth weight, risk of DM2, and lower insulin secretion in adults. However, it remains to be proven if they are related to fetal-neonatal insulin secretion or insulin resistance.
Methods
Genotyping for rs11708067 in *ADCY5* was performed by RFLPS and for rs7754840 in *CDKAL1* by qPCR with TaqMan probe in genomic DNA from 218 healthy neonates recruited in Guanajuato. Neonatal C-peptide and insulin concentrations were measured by ELISA. The difference between genotypes was evaluated using ANOVA. The association of polymorphisms with insulin and C-peptide was evaluated by multiple regression.
Results
Differences were found in the concentrations of insulin ($P=0.010$) and C-peptide ($P=0.004$) between rs11708067genotypes, with lower concentrations of both variables on allele A carriers. We found an inverse association of the A allele of rs11718067 with insulin ($P=0.016$) and neonatal C-peptide ($P<0.001$). No differences were found between genotypes and birth weight, glucose, or HOMA-IR. For rs7754840 no difference was found between genotypes for any variable, nor association with insulin concentrations or C-peptide.
Conclusions
The risk allele A in rs11708067 ADCY5 could be related to fetal/neonatal insulin secretion. This is the first study to evaluate neonatal insulin associated with the rs11708067 genotype. This proyect was supported by CONACYT (CB-2013-222563) and UG-DAIP 2016-2017 (1089/2016).

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Diabetes (to include epidemiology, pathophysiology)

P331

Evaluation of community pharmacy-based services for type-2 diabetes in an Albanian setting: pharmacist survey

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Background
Diabetes type II is an emerging chronic disease in developing countries. Currently the management of diabetes in developing countries is mainly hospital or clinic based. With burgeoning numbers of patients with diabetes, other models need to be evaluated for service delivery in developing countries. Community pharmacists are an important option for provision of diabetes care. Currently, data regarding practices of community pharmacists in diabetes care in Albania are limited.
Objectives
To evaluate current community pharmacy-based services and perceived roles of pharmacists in type 2 diabetes care, and characteristics (pharmacist and pharmacy) associated with current practice.
Setting
Community pharmacies in several cities in Albania.
Methods
A questionnaire was administered to pharmacists managing a random sample of 30 community pharmacies in different cities in Albania. Current practice and pharmacists' perceived roles were rated using Likert scales, whilst an open-ended question was used to identify priority roles. Logistic regression models determined characteristics associated with current practice.
Results
A response rate of 60% was achieved. Dispensing (100%) and education on how to use medications (72.6%) were common current pharmacy practices. More than 50% of pharmacists were supportive towards providing additional services beyond dispensing. The highest priorities for services beyond dispensing were education on medications [i.e. directions for use (58.6%) and common/important adverse effects (25.7%)], education on exercise (36.5%), education on diet (47.7%), and monitoring medication compliance (27.9%). Facilitators identified were: being perceived as part of a pharmacist's role (for all priority services), pharmacies with more than 50 diabetes customers per month (for diet education), and pharmacists' involvement in diabetes training (for compliance monitoring). The key barrier identified was lower pharmacist availability (for diet education as well as compliance monitoring).
Conclusions
Most community pharmacies in Albania have only provided a basic service of dispensing for type 2 diabetes patients. Many pharmacists believed that they should extend their roles particularly regarding patient education and monitoring. The development of pharmacist professional roles would assist in managing the burgeoning burden of diabetes. The identified facilitators/barriers provide baseline data to support the development of community pharmacy-based diabetes services.

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Estimation of HbA1c in hospitalized patients with bronchial asthma

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Background
Asthma is a chronic inflammatory respiratory disease. Stress hormones may increase in asthma and expected to induce hyperglycemia. Some anti-asthma medications increase blood glucose levels e.g. Beta-agonist, while others are known hyperglycemic agent's e.g. steroids. People who have experienced stress hyperglycemia during severe illness have a threefold risk of developing diabetes in subsequent years, and it may be appropriate to screen for diabetes in survivors of critical illness.
Aim
The aim of this study is to assess hyperglycemia patients with bronchial asthma, to the best of our knowledge; this is the first study to assess serum level of HbA1c among patients with bronchial asthma in Duhok, Iraq.
Methods
A case-control study conducted at the medical ward, department of internal medicine at Azadi Teaching Hospital in Duhok Governorate, Kurdistan Region, Iraq from 1st June 2016 to 30th January 2017. Seventy five patients and seventy five controls were enrolled in this study. HbA1c measurements were performed on blood samples of patients and controls.
Results
The study revealed that the rate of hyperglycaemia was higher in cases of bronchial asthma in comparison to healthy controls ($P=0.001$). Our data suggest that the HbA1c level were elevated in 26(34.6%) of patients and in 4(5.3%) of controls. Levels of HbA1c was not significant in chronic use of corticosteroid both inhaler and oral type, salbutamol inhaler, current use of corticosteroid both intravenously and orally, and duration of bronchial asthma ($P>0.009$).
Conclusion and recommendations
Hyperglycemic control might improve risk assessment in those patients with bronchial asthma. Measurement of RBS besides HbA1c in asthmatic patients is essential. Hyperglycemia more probably is associated with bronchial asthma itself rather than its treatments. In patients admitted to a medical ward with acute bronchial asthma, glucose levels should be monitored closely.

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P333

Inpatient diabetes management service, 30-day readmissions and length of stayof patients with diabetes

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Context
Diabetes mellitus (DM) is common among hospitalized patents. An inpatient diabetes management service (IDMS) has been implemented to provide better glycemic control. The impact on length of stay (LOS) and 30-day readmission rates is unknown.
Objective
We retrospectively analyzed LOS and 30-day readmission rate of patients with known DM admitted to a 240-bed community hospital in suburban Maryland between January 2016 and May 2017.
Methods
International Classification of Diseases 10 codes were used to identify patients with diabetes. LOS and 30-day readmissions were analyzed using Quality Advisor (SM) software. Data were compared by two-sample t-test and simple linear regression analysis.
Results
4654 patients with DM (71.32±13.95 years, 48.3% female) were admitted to a community hospital during the data collection period. IDMS team was consulted on 22.3% of the patients, while the remainder of patients with DM were cared for by other medical and surgical teams. Average LOS and 30-day-readmission rate in all patients decreased by 0.87 days and 10.52%, respectively, from January 2016 to May 2017. Average LOS of patients cared by IDMS team was higher, than control group (6.49 vs 4.72 days, $P=0.000000035$). There was no difference in 30-day readmission rates between the groups. Similarly, there was no difference in LOS trends between the two groups ($P=0.88$).
Conclusions
Since the implementation of IDMS team, LOS and 30-day readmission rate significantly decreased in all patients with diabetes at the community hospital. We speculate that patients with diabetes cared for by the IDMS team may have overall longer LOS, likely due to higher complexity and severity of illness. Limitation of this study includes confounding variables (e.g. mortality index), and a short time frame during which this study was conducted. Further studies are needed, including a formal cost effectiveness analysis, to better assess the economic impact of the IDMS team model in community hospitals.

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Evolution of the degree of glycemic control in a cohort of patients with type 2 diabetes mellitus. study to 26 weeks

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Objective
To evaluate the evolution of glycemic control in a cohort of patients with type 2 diabetes mellitus (T2DM) after its assessment in endocrinology.
Methods
Prospective cohort study. 465 patients with T2DM who were not followed up at an endocrinology clinic were included. This study was approved by the Ethics and Clinical Research Committee of the University Hospital of Guadalajara.
Results
Mean age was 63.4±12.5 years; 61.5% males. Time of evolution of T2DM was <5 years in 30.1% of cases and ≥5 years in 69.9%. At the beginning of the study, 7.5% of patients did not receive hypoglycaemic treatment, 60.9% received oral antidiabetics (OA) (including glucagon-like peptide-1 receptor agonists), and 31.6% received insulin therapy (with or without OA). Initial body mass index was 33.2±7.4 kg/m^2 and at 26 weeks follow up was 32.4±6.8 kg/m^2 ($P<0.0001$). Initially, 1.3% of the patients presented some episode of severe hypoglycaemia in the year prior to their inclusion in the study, while after 26 weeks of follow-up, 1.4% of the patients presented some episode ($P=0.7$).
Evolution of glycated hemoglobin (HbA1c) according to the characteristics of the patients. Initial HbA1c; HbA1c at 26 weeks of follow up; Difference of means; 95%CI; p.
– Entire cohort: 8.3±1.8; 6.6±0.9; 1.7; 1.4–1.9; <0.0001
– Male: 8.4±1.7; 6.6±1; 1.8; 1.6–2.1; <0.0001
– Female: 7.9±1.9; 6.6±1; 1.3; 1–1.8; <0.0001
– <65 years: 8.6±1.9; 6.5±1.1; 2.1; 1.7–2.4; <0.0001
– ≥ 65 years: 7.9±1.6; 6.7±0.9; 1.2; 1–1.5; <0.0001
– <5 years of evolution of T2DM: 8.2±2.1; 6.2±0.8; 2; 1.5–2.5; <0.0001
– ≥5 years of evolution of T2DM: 8.3±1.7; 6.8±1; 1.5; 1.3–1.8; <0.0001
– Initial HbA1c ≥7%: 9.1±1.6; 6.8±1; 2.3; 2.1–2.6; <0.0001
– Initial HbA1c <7%: 6.4±0.4; 6.2±0.8; 0.2; −0.002–0.3; 0.098
– Initial treatment with OA; 8.1±1.8; 6.5±0.9; 1.6; 1.3–1.9; <0.0001
– Initial treatment with insulin: 8.7±1.8; 6.9±1.1; 1.7; 1.3–2.1; <0.0001
Conclusions
– There is an improvement in glycemic control without weight gain or increase of severe hypoglycaemia episodes.
– The improvement is independent of the characteristics of the patients, although it is not achieved in patients with initial HbA1c <7%.

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Study of the association of transcription factor 7 like 2 gene polymorphism with type 2 diabetes mellitus and diabetic nephropathy in the Egyptian population

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Background
Studies from different parts of the world have given controversial results regarding the association of transcription factor 7like 2 (*TCF7L2*) gene polymorphism with Type 2 diabetes mellitus (T2DM) and diabetic nephropathy (DN). Aim: This study aimed to investigate if *TCF7L2* gene polymorphism, rs12255372(G>T) is a risk factor for the development of T2DM and DN in type 2 Egyptian diabetic patients. PATIENTS AND METHODS: This study was conducted on 150 subjects, divided into three groups (50 type-2 diabetic patients without nephropathy, 50 type-2 diabetic patients with nephropathy (DN) and 50 age and sex matched normal subjects). Genotyping for the rs 12255372(G>T) polymorphism in *TCF7L2* gene was performed by real time PCR. RESULTS: There was statistically significant association between *TCF7L2* gene polymorphism rs 12255372 and type 2 diabetic patients & DN, P=0.005, the allelic frequency differed significantly between the three studied groups P=0.005, denoting that the G allele was the risky allele for developing T2DM & DN. CONCLUSION: The present study indicates a strong association between *TCF7L2* variants and the risk of developing T2DM & DN and suggests a role of ethnicity and genetic background for susceptibility to diabetes and its complications.
Keywords: Type-2 diabetes mellitus – diabetic nephropathy – TCF7L2 Gene – single nucleotide polymorphism – real time PCR.

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Relationship between serum zinc, glycemic status and HOMA2 parameters in a regional Australian hospital population

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Aim
Previous studies demonstrated lower serum zinc among prediabetics and diabetics, compared to normoglycaemics. There is no current epidemiological data available in regional Australia examining the association between serum zinc and glycaemic status. This study was conducted to determine the relationship between serum zinc, glycaemic status and Homeostasis Model Assessment (HOMA-2) parameters in a regional Australian hospital population.
Methods
A retrospective review was conducted among all adult patients who presented to a regional Australian hospital between June 2004 and April 2017. Patients were included if they had either fasting blood glucose (FBG) and serum zinc; or FBG,

serum zinc and fasting insulin done. Serum zinc, FBG, fasting insulin, lipid profile, vitamin D and other demographic information were collected. Beta-cell function, insulin resistance and insulin sensitivity were calculated using the HOMA-2 calculator. All data were analysed using Stata 11.
Results
A total of 313 patients' record was retrieved. According to American Diabetic Association classification, 74.8% (234) were normoglycaemics, 18.8% (59) prediabetics and 6.4% (20) diabetics. Data for 84 patients were available tosarah calculate HOMA-2 parameters. Mean serum zinc was found to be lower in prediabetics than normoglycaemics (14.68 ± 3.05 vs 14.96 ± 4.01 uMol/l). In simple linear regression among all participants, higher serum zinc was associated with an increased insulin sensitivity (coefficient 2.67, 95% CI: -1.3 and 6.7), decreased insulin resistance (coefficient -0.03, 95% CI: -0.12 and 0.57) and decreased beta-cell function (coefficient -3.2, 95% CI: -6.2 and -0.2).
Conclusion
Consistent with the current literature, we observed lower serum zinc in prediabetics than normoglycaemics. Higher zinc levels are associated with greater insulin sensitivity and lower insulin resistance. Low serum zinc may have a role in the pathogenesis of insulin resistance. Further evaluations are warranted regarding zinc supplementation in prediabetics to prevent or delay the progression to Type 2 Diabetes.

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The role of polysomnography for detection of OSA in patients with type 2 diabetes in the Uzbek population

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Actuality
According to the International Classification of Sleep Disorders in type 2 diabetes, the risk of obstructive sleep apnea (OSA) in middle-aged people ranges from 18% to 36%. In a report by S. D. West et al. the incidence of sleep apnea in patients with diabetes is estimated at 23% compared with 6% in the general population. In a recent study, AS Peltier et al. it was found that 79.2% of patients with OSA had a violation of glucose tolerance and 25% were first diagnosed with diabetes mellitus. There is a high prevalence of type 2 diabetes and related metabolic disorders among patients with obstructive sleep apnea syndrome (OSAS). Sleep apnea has a negative effect on the function of the beta cells of the pancreas and insulin sensitivity.
Purpose
Detection of OSA by results of the Stop-bang questionnaire in patients with type 2 diabetes using polysomnography.
Material and methods
We interviewed 150 women on the Stop Bang questionnaire, 40 women had a high risk of developing OSA, patients underwent polysomnography for confirmation of OSA: average of age 52.7; IAG 56.4; BMI-32.4; Hb1C-7.9%; Desaturation-80.The same is divided by the severity of the course of OSA: low $5 \leq$ IAG, average < 15, $15 \leq$ IAG, high < 30 IAG ≥ 30.
Results
According to the results, low degree of OSA-11 (27%) in women, an average severity of OSA-12 (30%), a severe degree of 17 (42.5%) in patients with type 2 diabetes, OSA revealed obesity of grade 3 and a high level of Hb1C (8.1%). The results of the study show that OSA is independently linked to insulin resistance of glucose, thus can lead to increased blood sugar levels. The Stop Bang questionnaire is one of the promising methods for detecting OSA and direction patients for polysomnography. Patients were recommended to comply with HLS, the use of intraoral devices and CPAP therapy.

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Transcription Factor 7 Like2 Gene Polymorphisms and Susceptibility to Type 2 Diabetes Mellitus in a cohort of Egyptian diabetic patients, a pilot study

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Purpose
Transcription factor 7-like 2 (*TCF7L2*) variants are known risk factors of type 2 diabetes (T2DM).However; this association is not consistent among different populations. The current study aimed at investigating the relationship between rs 7903146, rs 12255372 variants of *TCF7L2* and susceptibility to T2DM.
Patients and methods
This case control study included 60 diabetic patients and 60 matched unrelated healthy controls. Genotyping was performed by using Real Time-PCR. The frequency of genotypes and alleles, anthropometric measures, glycemic indices, HOMA-IR and lipid profile were evaluated in patients and control.
Results
Regarding rs 7903146, TT genotype was more frequent in healthy controls (43.3%) than diabetic patients (20%) (OR = 0.291, 95% CI = 0.108–0.788, $P = 0.015$). T allele was more frequent in healthy control (61.7%) than diabetic patients (44.2%) and it was associated with lower risk of diabetes (OR = 0.492, 95% CI = 0.294–0.823, $P = 0.007$). In contrast, T allele of rs12255372 had no significant relation to diabetes risk (OR = 0.602, 95% CI = 0.361–1.005, $P = 0.052$). There was no statistically significant difference of frequency of any rs12255372 genotypes between cases and controls.
Conclusion
The study confirmed the association of *TCF7L2* (rs 7903146) and T2DM, while failed to detect any association between *TCF7L2* (rs 12255372) and susceptibility to T2DM.

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Undiagnosed diabetes and related risk factors in postmenopausal women: the 2011–2012 Korean National Health and Nutrition Examination Survey

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Aims
Postmenopause is associated with unfavorable metabolic disturbances and might be related to increase the risk of diabetes. Identification of undiagnosed diabetes and at-risk individuals may allow to initiate earlier management and to prevent diabetic complication. The objective of the present study was to determine the prevalence of undiagnosed diabetes and related risk factors in postmenopausal women.
Methods
This study was based on data from the Korean National Health and Nutrition Examination Survey (KNHANES), conducted during 2011-2012 by the Korean Ministry of Health and Welfare. This survey is a cross-sectional and nationally representative study of noninstitutionalized civilians using a stratified, multistage, clustered probability sampling design. From the 16,576 participants, data for 2,210 postmenopausal women were included in the analysis.
Results
The prevalence of undiagnosed diabetes in Korean postmenopausal women was 6.8%. They were older, more obese, under educated and the prevalence of hypertension and dyslipidemia was higher than the women without diabetes. The menarche age was later, but the age at menopause, breast feeding, oral contraceptive did not show significant difference. The multivariate logistic regression analysis showed that waist circumference over 80 cm (odds ratio [OR] 2.623 [95% CI 1.517-4.534]), hypertension(1.847 [1.120-3.045]), dyslipidemia(2.109 [1.314-3.383]) significantly increased the risk of undiagnosed diabetes. Moreover, women who had a two, or three components of metabolic syndrome were significantly associated with the risk of undiagnosed diabetes.
Conclusion
The prevalence of undiagnosed diabetes in Korean postmenopausal women was 6.8%. The components of metabolic syndrome were significantly associated with the risk of undiagnosed diabetes. Therefore individualized approach to postmenopausal women with components of metabolic syndrome is needed to early diagnose and manage diabetes.

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Comparison of quality of life and symptoms of depression in diabetes combined with gastroparesis and without it

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Objective
To assess the quality of life, the presence and severity of depressive symptoms in patients with diabetes combined with gastroparesis and without it
Methods
Forty three patients with diabetes were included in the study. The presence and severity of gastrointestinal symptoms, as well as the intensity and frequency of symptoms over the last 2 weeks, were measured with the Patient Assessment of the upper gastrointestinal symptom severity index (PAGI-SYM), the Patient Assessment of the upper gastrointestinal disorders-quality of life (PAGI-QOL). To assess the emotional sphere and cognitive functions, questionnaires were used: 36-item Short Form Health Survey and Beck Depression Inventory.
Results
In our study, a significant prevalence of GI symptoms among patients with diabetes was found: 24 patients had gastrointestinal symptoms (55.8%), 19 patients had no such symptoms (44%). In our study, we compared the prevalence of depression in a group of patients with GI symptoms and without them: in both groups there was a mild degree of depression (10–15 points in the assessment of the Beck Depression Inventory), in 8 patients with GI symptoms (33%) there was a moderate degree of depression (16–19 points), the severity of gastrointestinal disorders in patients with diabetes did not correlate with the severity of depression in these patients. In the analysis of the SF-36 QoL questionnaire, the median QoL in patients with diabetes without GI symptoms ranged from 50 (general health) to 100 (role-related emotional functioning). In the group of patients with GI symptoms, the median of quality of life scores on 8 scales ranged from 45 (general health) to 70 (physical functioning, social functioning). When comparing groups of patients, significant differences in glycemic control were not revealed, and according to the results of testing, lower values of the quality of life in the group with GI symptoms were noted. Both groups reported deterioration in the quality of life, but the severity of the symptoms of depression was greater in the group with GI symptoms.
Conclusions
Patients with diabetes and symptoms of gastroparesis suffer from deterioration in the quality of life and the severity of depressive symptoms.

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Predictors of anxiety development at diabetes mellitus type 1

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Objective
To assess possible predictors of anxiety disorder development at Diabetes Mellitus type 1.
Materials and methods
There were examined 164 patients (93 males and 71 females) with diabetes mellitus type 1 (DM) at the age from 18 to 60 years old. The level of anxiety was assessed with the use of the Hospital Anxiety and Depression Scale (HADS), blood glucose level was determined in the fasted state and 2 hours after the meal. Also there was monitored average daily glucose in blood during 3 days at fourfold detection of glycemia; there were detected glycated hemoglobin level (HbA_{1C}), total cholesterol (TC), triglycerides (TG), very low-density lipoprotein cholesterol (VLDL cholesterol), low-density lipoprotein cholesterol (LDL cholesterol), high-density lipoprotein cholesterol (HDL cholesterol), blood homocysteine level.
Results
1. There were determined anxiety disorders within 30,48% patients with DM type 1.
2. The growth of average glycemia significantly increased the risk of development of anxiety disorders (b = 0,16) (Exp (b) = 1,18; 95% CI – 1,03 ÷ 1,34; $P < 0,02$).
3. The risk of anxiety disorder development is not associated with levels of total cholesterol (b = 0.20) (Exp (b) = 1.23; 95% CI – 0.93 ÷ 1.60; $P = 0.09$), level of total VLDL cholesterol (b = 0.55) (Exp (b) = 1.73; 95% CI – 0.87 ÷ 3.46; $P < 0.10$), level of AC (b = 0.20) (Exp (b) = 1.22; 95% CI – 0.92 ÷ 1.62; $P < 0.10$) and level of homocysteine (b = 0.64) (Exp (b) = 1.07; 95% CI – 0.99 ÷ 1.15; $P = 0.08$).

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Comparative analysis of the prevalence of type 2 diabetes according to the screening and register data in Uzbekistan

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Purpose of the study
To carry out the comparative analysis of the prevalence of Type 2 Diabetes (T2DM) according to the screening and register data in Uzbekistan.
Material and methods
Within the framework of WDF international project 'Prevention of diabetes in rural population of Uzbekistan', with the support of the Ministry of Health of the Republic of Uzbekistan, the screening campaign was conducted in 6 rural regions to actively identify diabetes and IGT among 6189 people at high risk. A questionnaire chart (developed on the basis of FINDRISS map, taking into account the mentality of the Uzbek people) included the following risk factors: age; Excess weight or obesity; Arterial Hypertension; Myocardial infarction; Stroke; Birth of a child weighing >4 kg. The average age is 59.39 ± 10.22 years, 62% of women and 38% of men. 6189 people passed the GTT and HbA1c tests. Statistical data processing was made using the program Statistica 10, Excel (2007).
Results of the study
Following the results of fasting glycemia (venous blood) and OGTT, T2DM was detected in 823 people (13.3%), including 548 women, 275 men (ratio 2:1). Newly diagnosed peoples with diabetes have already HbA1c level such as: HbA1c >6.5–23.4%; between 8–9% and >9%–12.7%, that indicating long-term hyperglycemia and an advanced stage of the disease which can lead to the further development of diabetes complications. The IGT was found in 26.7%, IFG in 1040 people accordingly. The frequency of T2DM in the peoples at high risk was 16,3% which is significantly higher than the officially registered prevalence of diabetes in Uzbekistan (5–6%). It demonstrates once again low level of diabetes diagnosis and duly treatment at the primary healthcare link. The prevailing risk factors for diabetes development among the rural population were: Arterial Hypertension-78.6%; Obesity (BMI >30) – 43.3%, Gestational diabetes –42%, hereditary predisposition –35.2%.
Conclusion
The screening undertaken in 6 regions identified a high level of the high prevalence of T2DM in the high-risk group (13.3%) compared with the national register of 5–6%. These figures reveal the importance of screening to actively detect the people with diabetes, IGT and IFG in order to provide the appropriate treatment and prevent the development of serious complications. The prevailing risk factors for diabetes development among the rural population aged over 40 years in Uzbekistan were: arterial hypertension – 78.6%; obesity (BMI >30) – 43.3%, gestational diabetes – 42%, hereditary predisposition – 35.2%.

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Nutrition of non-fasting patients with diabetes during the month of Ramadan

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Introduction
Fasting during the month of Ramadan is the most observed religious practice by Muslims. Diabetes is one of the condition that exempt Muslims from fasting because of the risk of complications. The International Diabetes Federation states that high-risk patients 'should not fast'. The objective of this study was therefore to evaluate the daily food intake during the month of Ramadan in non-fasting patients with diabetes in order to detect diet mistakes made during this month.
Patients and methods
Descriptive study conducted in 66 patients with diabetes.
Results
The average age was 51,33 years with a sex ratio of 0,5. Twenty-two patients had type 1 diabetes and 44 patients had insulin-requiring type 2 diabetes. During the month of Ramadan the average daily intake in Kcal increased by 6,7% ($P = NS$). There was a significant increase in protein intake at the expense of animal protein

($P=0.019$); a significant increase in lipid intake with increased cholesterol intake ($P=0.002$) and a decrease in carbohydrate intake despite a significant increase in sucrose consumption ($P=0.008$). The diet was low in fiber, iron, magnesium and folic acid with a significant increase in calcium intake ($P=0.005$). In addition, there was a poor distribution of meals, with a decrease in breakfast and lunch, in favor of dinner, which corresponded to '*el iftar*' (*P* respectively 0.027, 0.001 and 0.024).

Conclusion

The results of our study reflect the nutritional errors made by our patients during Ramadan. These data testify to the complexity of diabetes management which is difficult even in normal times. A preparation before Ramadan and a continuous educational approach are recommended, with an educational support adapted to the local context during the holy month.

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Evaluation of procalcitonin levels in diabetic and diabetic nephropathic patients

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Aim

To determine how serum procalcitonin (PCT) levels are affected in diabetic and diabetic nephropathic patients, it is important to determine whether PCT is indicative of an inflammation in these patients.

Materials and methods

The study included 175 patients (75 diabetic nephropathy (group 1), 75 diabetic (group 2) and 25 non-diabetic nephropathy (group 3)) and 75 healthy volunteers. Serum and urine creatinine, serum high sensitive C- reactive protein (HsCRP), procalcitonin, white blood cell, neutrophil, HbA1c and urinary protein values of patient and control groups were obtained. Urinary protein / creatinine ratio and eGFR were calculated.

Results

There was no significant difference between groups 1, 2, 3 and control group of the PCT values (0.20, 0.19, 0.23 and 0.19, respectively) ($P>$ 0,05). HsCRP levels of all 3 patient groups were higher than the control group ($P<0.001$). There was a negative correlation between eGFR values of nephropathy patients (diabetic and non-diabetic) and PCT ($P<0.001$; $r=-0.475$) and HsCRP ($P<0.001$; $r=-0.415$) values. When diabetic nephropathy patients were compared with those below eGFR 60 and those above eGFR 60, When the eGFR values were lower than 60, the HsCRP values were higher ($P<0.05$); There was no difference between the PCT values ($P>0.05$).

Conclusion

There was no significant increase in PCT values of diabetic and diabetic nephropathy patients. However, there was a negative correlation between PCT level and eGFR.

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Telmisartan increases gluconeogenesis by inducing PKCζ-Thr^{410} phosphorylation in hyperglycemia-treated HepG2 cells and high-fat diet-fed mouse liver

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Telmisartan, an angiotensin II type 1 receptor blocker (ARB), is widely prescribed for the treatment of hypertensive patients with simultaneous diabetes mellitus (DM). Unlike other ARBs, telmisartan is reported to have various ancillary effects as well as common blood pressure-lowering effect. In this regard, telmisartan improves endothelial dysfunction and cardiovascular complications in DM patients and is recently reported to reduce new-onset DM incidence. However, effects and mechanism of telmisartan on gluconeogenesis in hepatocytes and liver remain elusive. Here, we investigated effects and a molecular mechanism of telmisartan on gluconeogenesis in hyperglycemia-treated HepG2 cells and high-fat diet (HFD)-fed mouse liver. Telmisartan dose-dependently increased gluconeogenesis in hyperglycemia-treated HepG2 cells and accompanied an increase of phosphoenolpyruvate carboxykinase (PEPCK) expression without change of glucose-6-phosphatase (G6Pase) expression. Furthermore, telmisartan dose-dependently increased insulin receptor substrate-1 (IRS-1)-Ser^{302} phosphorylation and decreased IRS-1-Tyr^{632} phosphorylation, indicating that telmisartan impairs insulin action in HepG2 cells. Because protein kinase C ζ (PKCζ) is reported to reduce insulin action by inducing IRS-1 serine phosphorylations, we assessed its phosphorylation and found that telmisartan dose-dependently increased PKCζ-Thr^{410} phosphorylation. Ectopic expression of dominant-negative PKCζ constructs significantly attenuated the telmisartan-induced gluconeogenesis and the telmisartan-induced IRS-1-Ser^{302} phosphorylation and -inhibited IRS-1-Tyr^{632} phosphorylation, although it did not alter PEPCK expression, showing that gluconeogenesis, when insulin is acutely treated, is largely regulated by changes of IRS-1 phosphorylations. Among ARBs, including losartan and fimasartan, only telmisartan induced IRS-1-Ser^{302} phosphorylation and decreased IRS-1-Tyr^{632} phosphorylation. Furthermore, effects of telmisartan on IRS-1 phosphorylations were not altered by pretreatment with GW9662, a specific and irreversible peroxisome proliferator-activated receptor γ antagonist. Finally, in the liver from HFD-fed mice, telmisartan increased PEPCK and G6Pase expressions and PKCζ-Thr^{410} phosphorylation, and accompanied an increase and a decrease of IRS-1-Ser^{302} and -Tyr^{632} phosphorylations, respectively. Taken together, our findings suggest that telmisartan increases gluconeogenesis by inducing PKCζ-Thr^{410} phosphorylation that leads to increased phosphorylation of IRS-1-Ser^{302} and decreased phosphorylation of IRS-1-Tyr^{632}, and consequently impairs insulin action in hepatocytes.

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Diabetes complications and comorbidities in patients newly diagnosed with diabetes in newfoundland and labrador (NL): gender differences

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Introduction

Diabetic patients are known to develop complications and co-morbidities as a result of the disease. Determining gender susceptibility to diabetic complications can lead to improved patient-centered care for patients.

Objectives

To examine the gender differences on complications and comorbidities in patients newly diagnosed with diabetes in NL.

Methods

A retrospective cohort study, patients were followed for 5 years from the date of diagnosis, between 1998 to 2003, till their deaths or end of study (2008), whichever came first. The study included individuals who were newly diagnosed with diabetes aged 20 years and older that were identified using provincial medico-administrative data. Gestational diabetes was excluded. Diabetes complications and comorbidities were defined as any record for cardiovascular disease, renal failure, end stage renal disease and lower-extremity amputation during the study period. Late diagnosis was identified as any record for complications at the time of diagnosis. Other variables included healthcare utilization and place of residence. Healthcare utilization was defined as number of visits with family physicians, specialists as well as number of hospitalizations per year. Descriptive analyses as well as multiple logistic regressions were performed.

Results

There were 20,292 patients, mean age 60($\pm$15); 50% were women. Majority of the patients (63%) belonged to urban areas. Approximately, 17% of the men and 13% of the women had a late diagnosis ($P<0.000$). Five year after diagnosis, 27% and 18% of men and women respectively had at least one complication, while 18% of men and 16% of women had died during the study period. Men were more likely to develop diabetic complications than women (OR = 1.63, CI 1.51–1.75) after being accounted for age, late diagnosis, place of residence and healthcare utilization.

Conclusion
Men are prone to late diagnosis and developing more diabetic co-morbidities than women in NL. The differences in the healthcare utilization and the susceptibility to late diagnose in males can account for the differences observed between gender. Therefore, the gender differences in health and healthcare should be taken into account in diabetes management. Further research is required to determine the biological and healthcare factors.

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Visfatin concentration and anthropometric/biochemical parameters in healthy individuals-preliminary study

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Visfatin (pre-B cell colonyenhancing factor) is a adipocytokine playing an important role in glucose homeostasis. High concentrations of visfatin are observed in obese people. Previous studies suggest that estimation of visfatin concentration could be a promising tool for predicting obesity or its metabolic consequences. The aim of the study was to evaluate the correlation between visfatin concentration, selected anthropometric parameters (BMI, WHR, BAI, VAI index) and biochemical parameters (glucose metabolism parameters). 39 patients without carbohydrate metabolism disorders, diagnosed at endocrinology department because of other reasons were included to the study. The exclusion criteria were any glucose metabolism disorders (diabetes mellitus, insulin resistance, glucose intolerance, fasting glucose impairment) or medications influence glucose concentration and metabolism (glucocorticosteroids, hypoglycaemic drugs, etc.). The data were statistically analyzed by STATISTICA. $\alpha=0.05$. The median age was 33 years (26–38 years). 69% patients with normal weight (n = 27), 21% patients overweight ($n=8$) and 10% obese ($n=4$). The median BMI was 23.7 kg/m^2 (21.1–26.5 kg/m^2); WHR 0.8 (0.75-0.85); BAI 29% (25-32%); VAI 0.87 (0.61–1.29). The median serum visfatin was 0.7 ng/ml (0.4–5.6 ng/ml); fasting insulin 6.7 μU/ml (5.5–9.1 μU/ml); fasting glucose 88 mg/dl (84–93 mg/dl). There were no correlation observed among differences in visfatin concentration (0.7 vs 0.8 vs 0.9, $P=0.8$) was found between patients of examined groups (respectively patients with normal weight, overweight and obesity) as well as no correlation between visfatin concentration in relation to fasting glucose ($R=-0.1$, $P=0.5564$); fasting insulin ($R=-0.09$, $P=0.5662$) was observed. Moreover, not significant correlation of BMI and visfatin levels ($R=0.06$, $P=0.7192$), WHR index and visfatin levels ($R=0.11$, $P=0.5071$), BAI index and visfatin levels ($R=0.01$, $P=0.9571$) as well as VAI index and visfatin ($R=-0.09$; $P=0.5913$) were observed. Visfatin concentration in healthy individual does not correlate with anthropometric parameters and glucose parameters.

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Serum soluble vascular adhesion molecules and highly sensitive C: reactive protein in elderly type 2 diabetic patients with mild cognitive impairment

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Background
T2DM is a metabolic disorder characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency with disturbances of carbohydrate, fat, and protein metabolism.T2DM is a risk factor for Alzheimer's disease and mild cognitive impairment. The etiology of cognitive impairment in people with T2DM is uncertain, but it is most likely multi factorial. Chronic hyperglycemia, cerebral micro vascular disease, severe hypoglycemia, and increased prevalence of macro vascular disease are implicated.
Aim of the work
To determine the serum levels of soluble vascular adhesion molecule (sVCAM-1) and highly sensitive C-reactive protein (hs-CRP) in elderly type 2 diabetics with mild cognitive impairment (MCI).
Patient and methods
Our study was conducted on 90 elderly subjects (aged 60 years old or more). They were divided into Group I, 30 patients with T2DM and mild cognitive impairment, group II, 30 patients with T2DM without cognitive impairment and group III, 30 healthy subjects as a control group. All participants were subjected to history taking, full clinical examination, anthropometric measurement, the Addenbrooke's Cognitive Examination III (ACE–III 2012) and laboratory investigations including Fasting plasma glucose, 2 hours plasma glucose, HbA1c, serum cholesterol, triglycerides, LDL-c, HDL-c, protein/creatinine ratio, serum sVCAM-1 and hs-CRP.
Results
Serum levels of sVCAM-1 in diabetic elderly patients with MCI were significantly higher (946.7 ± 162.01 ng/ml) than diabetic elderly patients without cognitive impairment (479.06 ± 65.27 ng/ml) and control (263.7 ± 72.05 ng/ml) with ($F=0.652$ and $P=0.002$). Serum levels of Hs-CRP in diabetic elderly patients with MCI were significantly higher (7.9 ± 1.09 ng/ml) as compared to diabetic elderly patients without cognitive impairment (4.3 ± 0.96 ng/ml) and control (2 ± 0.74 ng/ml) with ($F=1.033$ and $P=0.005$).
Conclusion
Elderly diabetic patients with mild cognitive impairment, have higher levels of soluble adhesion molecules and markers of low-grade systemic inflammation than other groups. Inflammatory mediators play a role in the development of mild cognitive impairment in diabetic elderly patients.
Keywords: Diabetes Mellitus, Highly sensitive C-reactive protein, soluble vascular adhesion molecule, Mild Cognitive Impairment, Elderly

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Evaluating quality of diabetic care in patients with severe mental illness (SMI) in an academic primary care clinic

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Background
Higher prevalence of type 2 Diabetes Mellitus (DM II) has been reported in patients with SMI (serious mental illness). SMI patients get suboptimal diabetes care as compare to non- SMI patients.
Methods
We tested the hypothesis that SMI patients get suboptimal diabetes care as compare to non- SMI patients. We did a retrospective cohort study in an academic, primary care clinic for underserved,urban population.SMI patients included schizophrenia and bipolar disorder diagnosed by psychiatrist. We created electronic database of variables of interest for eligible patient population. Inclusion criteria included patients ages 18–75, and have been seen by a primary care provider for at least 1 year with at least 2 visits and at least 2 HbA1c levels between the study period. 184 SMI patients met the inclusion criteria; and were compared to 184 patients of non-SMI patients. Patients being treated by an endocrinologist for DMII were excluded from the study. Outcomes measures including HbA1c, blood pressure, LDL, eye and foot exam, nephropathy assessment and smoking status; and process measures such as alcohol and substance abuse, medications, pneumonia vaccine and health care utilization measures were measured and compared between two groups.
Results
Data analysis was done using logistic regression. After controlling for possible confounders such as gender, Race, BMI and Insulin use, there was no significant difference in HbA1C control of <7 between SMI and non-SMI groups ($P=0.115$). Patients who were on insulin therapy were less likely to achieve HbA1c <7 without any significant difference between SMI and non-SMI groups (12.5% vs 11.8%). However SMI patients who were not on insulin were more likely than non-SMI patients to achieve HbA1C <7 (75.3% vs 63.2%, OR = 3.26, 95% CI: 2.05–5.19, $P<0.001$). No significant between group difference was observed in remaining parameters of nephropathy assessment, blood pressure, foot exam, smoking cessation treatment offered except for eye exam (OR = 1.90, 95% CI: 1.08–3.34; $P=0.027$). There was no significant difference

in above parameters after adjusting for Antipsychotics use. There was no significant difference between the groups for number of clinic visits or continuity of primary care provided.
Conclusion
Diabetes care of SMI patients is not suboptimal to non- SMI patients in primary care clinic. Further study is needed to evaluate whether living in a supervised group home facility of SMI patients contributes improved care of SMI patients observed in our clinic.

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Prorenin and secreted frizzled-related protein-4 levels in women with gestational diabetes mellitus

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Background
This study was designed to investigate prorenin and secreted frizzled-related protein-4 (SFRP-4) levels in pregnancies with or without gestational diabetes mellitus (GDM).
Materials and methods
A total of 76 pregnant women were included in the study. Thirty-five of the pregnant women were included in the GDM group according to the results of oral glucose tolerance tests (OGTT) and 41 pregnant women were included in the control group.
Results
In the group with GDM, SFRP-4 value was found to be significantly higher than that of the control group (5.59 ± 3.32 ng/ml vs 4.05 ± 2.15 ng/ml; $P = 0.017$). Women with GDM had significantly higher serum prorenin levels compared with control group (737 (427–1339) pg/ml vs. 535 (376–725) pg/ml, $P = 0.009$). There was a significant positive association between prorenin and SFRP-4 levels in the GDM ($r = 0.91$, $P < 0.001$) and control group ($r = 0.42$, $P = 0.002$) and whole pregnancies ($r = 0.75$, $P = 0.002$).
Conclusions
We have shown that prorenin and SFRP4 were significantly elevated in GDM patients when compared to healthy control group. Furthermore, we found that there was a positive correlation between prorenin and SFRP-4.

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Novel inflammatory pathways in monocytes of type 2 diabetes patients are modulated by vitamin D

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Type 2 diabetes (T2D) patients have a high cardiovascular risk due to vascular inflammation and dyslipidaemia. Furthermore vitamin D (VD) deficiency is highly prevalent. Our aim was to elucidate the role of fatty acid receptors in inflammatory pathways and their regulation by VD. We therefore examined the VD effect on gene expression of Arachidonate 5-lipoxygenase (ALOX-5) and Sphingosine-1-phospate receptors (S1PR1 and S1PR2) in primary isolated monocytes of T2D patients and healthy controls (HC). $CD14^+$ monocytes (Mo) were isolated from 20 healthy controls (HC) and 20 T2D patients and were treated for 24 h with / without 10^{-8} M calcitriol. Interleukin-1β as an inflammatory stimulant served as IL-$1\beta_{control\text{-}cells}$. CD14, ALOX-5, $S1PR_1$ and $S1PR_2$ mRNA expression levels were measured by TaqMan™ analyses. 18s rRNA served as a house keeping gene. Gene expressions were defined as $2^{-[Ct\ (target)-Ct\ (18srRNA)]}$. Calcitriol treatment significantly increased the CD14 gene expression in both HC ($CD14_{calcitriol}$: 5059 vs. 2104; $P = 0.05$) and T2D ($CD14_{calcitriol}$: 12176 vs. 6712; $P = 0.001$) compared to the IL-$1\beta_{control\text{-}cells}$. The CD14 gene expression was noticeable increased in T2D patients compared to HC ($P = 0.002$). Moreover ALOX-5 mRNA-levels were also increased by calcitriol compared to the IL-$1\beta_{control\text{-}cells}$ in HC ($ALOX\text{-}5_{calcitriol}$: 1686 vs. 1004; $P = 0.02$) and in T2D ($ALOX\text{-}5_{calcitriol}$: 2744 vs. 1372; $P = 9.1 \times 10^{-5}$). By comparing HC vs. T2D, it stands out that ALOX-5 mRNA-levels were higher in T2D patients compared to HC ($P = 0.01$). Furthermore, the mRNA levels of $S1PR_2$ were significantly reduced in both HC ($S1PR_{2calcitriol}$: 5.75 vs. 25; $P = 10^{-6}$) and T2D ($S1PR_{2calcitriol}$: 5.96 vs. 36; $P = 0.001$) compared to the IL-$1\beta_{control\text{-}cells}$. Interestingly, T2D patients mRNA levels of $S1PR_2$ of IL-$1\beta_{control\text{-}cells}$ compared to HC were significantly higher ($P = 0.03$). Calcitriol treatment did not change the mRNA levels of $S1PR_2$ by comparing HC vs. T2D. No significant changes of the $S1PR_1$ mRNA expression were observed in calcitriol treated Mo from HC and T2D patients. *In vitro* calcitriol increased the CD14 and ALOX-5 gene expression in HC and T2D-patients.However, the increase of CD14 and ALOX-5 gene expression in T2D appears to be disease specific. Further calcitriol had no impact on $S1PR_1$ -but on $S1PR_2$ mRNA expression. Although calcitriol reduced the gene expression of $S1PR_2$ both in T2D-patients and HC this was not discriminatory. These results provide novel insights into potential anti-inflammatory mechanisms of VD in type 2 diabetes.

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Serum adiponectin in male type 2 diabetic patients exposed to ionizing radiation in early years

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Prevalence of diabetes mellitus in the world is constantly increasing and today the type 2 diabetes pandemic is the point of issue. The type 2 diabetes incidence in exposed individuals i.e. the participants of the Chernobyl Nuclear Power Plant accident consequences clean-up works (ChNPP ACUW) in Ukraine in the post-accident years was about 15-21%, which was significantly higher ($p < 0.0001$) than in the non-irradiated persons (3-9%). The adipose tissue is actively involved in regulation of the energy metabolism being the endocrine and paracrine organ producing a wide spectrum of adipocytokines. Adiponectin is the main adipotocytokine with cardioprotective effect but its role in the development of type 2 diabetes has not been studied in subjects exposed to ionizing radiation. The 66 male diabetic patients who were exposed to ionizing radiation after the Chernobyl catastrophe, 45 irradiated subjects having no diabetes, and a control group of 20 healthy persons were examined. Concentrations of the total adiponectin were significantly lower ($p < 0.05$) in blood serum of irradiated persons, namely in the ChNPP ACUW of the iodine period (first months upon the accident in 1986) who had the established diagnosis of type 2 diabetes being of a normal body weight, overweight or obese compared to the concentrations in the almost healthy subjects and the clean-up workers with normal glycemic control. Concentration of the total adiponectin decreased with increasing body weight, and there was a correlation of average strength between the concentration and obesity ($t = -0.367$, $p < 0.05$). With deterioration of glycemic control the concentration of total adiponectin decreased. With increase in disease duration from 5 to 20 years there is a slow decrease in total adiponectin concentration in blood serum in the ChNPP ACUW and in the control group. However, in disease duration over the 20 years there is an increase in the total adiponectin level. There were no significant differences in total adiponectin concentration with increasing the external exposure doses in the range of 10.0-860.0 mSv.
Conclusion
In men exposed at a young age due to the Chernobyl Nuclear Power Plant accident, which were the clean-up workers suffering diabetes mellitus a marked decrease in adiponectin concentration was observed in comparison with the same workers having no diabetes and with non-irradiated subjects. The adiponectin level depended on disorders of carbohydrate metabolism, body weight increase, and prolonged course of diabetes mellitus.

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Decreased spexin levels in patients with type 1 diabetes

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Spexin is a novel peptide which has a potential role as a biomarker of insulin resistance, diabetes and obesity. We aimed to investigate spexin levels in lean type 1 diabetes patients and spexin's role on glycemic parameters without the presence of obesity or insulin resistance.
Patients and methods
This cross-sectional study included 29 type 1 diabetic patients and a control group of 23 healthy subjects adjusted for age, sex and body mass index (BMI). Height and weight for every patient were measured using standard techniques. Glucose levels triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, serum cortisol levels and spexin levels were measured for each patient.
Results
Serum spexin levels were significantly lower in patients with type 1 diabetes than control subjects ($P=0.008$). Spexin levels were not correlated with glycemic parameters, lipids, BMI, cortisol levels and TSH ($P>0.05$). Only age was turned out to be correlated with spexin levels in patients with type 1 diabetes when groups are analyzed separately. Regression models including age and diabetes duration revealed no association between age and spexin levels. Regression models including cortisol, BMI, HbA1c revealed no association with spexin levels within each group.
Conclusion
In conclusion presence of type 1 diabetes results in lower spexin levels independent of glucose, lipid parameters and BMI. Its expression from pancreas apart from current glycemic control of the patients may be the main determinant of spexin levels in type 1 diabetic patients.

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Increase in C-peptide levels after short term glycemic control in patients with type 2 diabetes mellitus: myths or facts?

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Introduction
Long term control of glucotoxicity has been shown to increase the secretion of insulin and C-peptide (Cp) from beta cells. However, there is limited data concerning the effect of short term glycemic control and reversal of glucotoxicity on basal Cp. We aimed to investigate the change in serum Cp levels after short term glycemic control in patients with uncontrolled type 2 diabetes mellitus (DM).
Materials and methods
A total of 123 patients with type 2 DM admitted and hospitalized to our clinics with uncontrolled hyperglycemia were included. Demographic and clinical data, and basic laboratory parameters were recorded and analyzed. Basal fasting Cp levels were measured both at admission (Cp-admission) and after control of hyperglycemia just prior to discharge (Cp-discharge). Cp-difference was calculated as (Cp-discharge)-(Cp-admission). The patients were divided into 2 groups: group 1 with positive Cp-difference; group 2 with negative Cp-difference.
Results
Of the patients, 61.8% had positive Cp-difference, and Cp-differences were 0.16 ($\pm$1.59) ng/mL in all patients, 0.96 ($\pm$1.03) in group 1, and $-$1.11 ($\pm$1.51) in group 2 ($P=0.001$). Mean body weight, creatinine and Cp-discharge were significantly higher in group 1 ($P=0.045$, $P=0.013$, $P=0.00$; respectively). However, mean age, body mass index (BMI), diabetes duration, hospitalization duration, proteinuria, fasting and postprandial glucose, HbA1c, lipids, TSH, free T4, Cp-admission were similar in both groups. The patients were further subgrouped according to age ($65<$ or ≥ 65), BMI(<30 or $\geq 30 kg/m^2$), diabetes duration, use of secretagogue, diabetic ketaoacidosis history, HbA1c (<10 or $\geq 10\%$), hyperlipidemia or hypertriglyceridemia, presence of any microvascular complication. There were no significant differences between subgroups as regards to Cp-difference. Cp-admission was positively correlated with triglyceride, body weight and Cp-discharge ($P=0.004$, $P=0.025$, $P=0.00$; respectively); and negatively correlated with diabetes duration, HbA1c, and Cp-difference ($P=0.009$, $P=0.043$, $P=0.00$; respectively). Cp-discharge was positively correlated with triglyceride, body weight, Cp-admission and Cp-difference ($P=0.001$, $P=0.00$, $P=0.00$, $P=0.00$; respectively). Cp-difference was correlated positively with Cp-discharge ($P=0.00$), negatively with Cp-admission ($P=0.00$). Positive predictors of having positive Cp-difference were history of cardiovascular disease ($P=0.004$; Odds Ratio (OR)$=3$), and higher Cp-discharge ($P=0.00$; OR$=6.42$).
Conclusion
Our results indicate that short-term glycemic control has little but significant positive effect on basal Cp. Having cardiovascular disease was found as a strong predictor for positive Cp-difference. Presence or absence of microvascular complications, HbA1c level, and diabetes duration did not affect Cp-difference.

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Incidence of glucocorticoid-induced hyperglycemia among hospitalized nondiabetic patients

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Introduction
High-dose glucocorticoid therapy is a recognized cause of hyperglycemia. Given the paucity of literature regarding the incidence of glucocorticoid-induced hyperglycemia among nondiabetic patients, we commenced this study in order to assess its incidence and to identify risk factors.
Design
A retrospective longitudinal cohort study.
Methods
We retrieved patients over 18 years old, without prior diabetes diagnosis or treatment who were hospitalized in Rambam Health Care Campus between 1.1.2012 – 31.3.2017, and received $\geq$10 mg oral prednisone or equivalent intravenous hydrocortisone or intravenous dexamethasone, for at least 2 days. Demographic and laboratory values of patients who developed hyperglycemia (defined by $\geq$ 1 capillary blood glucose $\geq$ 180 mg/dl during the first 4 days of glucocorticoid treatment) were compared to those of patients who did not develop hyperglycemia.
Results
There were 671 patients who filled the inclusion criteria: 355 received oral prednisone, 164 received intravenous dexamethasone, and 152 received intravenous hydrocortisone. The incidence of glucocorticoid-induced hyperglycemia among all patients was 22.6%. Patients who developed glucocorticoid-induced hyperglycemia were older and had a higher creatinine, BUN and WBC count. Using multivariate regression analysis, age over 80 years (OR: 6.27, 95% CI 3.02-13.05), hospitalization in non-surgical wards (OR: 3.08, 95% CI 1.64–5.81), and a 4-day cumulative prednisone dose $>$ 240 mg (OR: 1.78, 95% CI 1.2–2.64), were identified as independent risk factors for hyperglycemia.
Conclusion
Older patients without prior diabetes receiving high doses of glucocorticoids should be monitored closely for the development of glucocorticoid-induced hyperglycemia. Special attention should be paid to patients receiving over 60 mg prednisone/day and patients hospitalized in non-surgical departments.

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Diabetes after liver transplantation

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Objective
Diagnosis of diabetes after transplantation (NODAT) has been described in up to 25% of cases. NODAT is a metabolically complex disorder, similar to type 2 diabetes. Factors that influence the development of NODAT are: BMI, HCV and immunosuppression. Objective: to know the prevalence and incidence of diabetes mellitus (DM) in liver transplant patients of our hospital.
Patients and methods
Retrospective descriptive study of liver transplant patients. Variables analyzed: age, sex, cause of liver disease, BMI, pretransplant DM, NODAT according to

ADA criteria and death. Statistical analysis: comparison of means with Student's T and proportions using chi-square statistics, statistical program SPSS v.18 for Windows.
Results
Liver transplantation in 73 patients (85% men). Age: 54.5±7.1 years. Liver disease: alcoholic cirrhosis 44.4%; cirrhosis HCV 22.2%; cirrhosis HBV 6.3%; alcoholic cirrhosis and HCV 12.7%; alcoholic cirrhosis and HBV 4.8%; another 9.6%. BMI: women 23.7±5.2 vs men 27.4±4.3 Kg/m^2 ($P=0.3$). BMI higher in group of alcoholic cirrhosis (28.5±5.2 Kg/m^2, $P=0.4$). Prevalence of pretransplant DM was 32% (alcoholic cirrhosis 40%, cirrhosis HCV 30%, alcoholic cirrhosis and HCV 10%, $P=0.9$). Prevalence of NODAT was 38% (alcoholic cirrhosis 45.8%, cirrhosis HCV 29.2%, alcoholic cirrhosis and HCV 8.3%, $P=0.9$). No remission of pretransplant DM. Incidence of NODAT was 11.6%, lower than that described in other series ($P=0.05$). 33.3% hepatocarcinoma in transplanted patients, 47.6% with DM (NODAT 20%). Transplanted deceased 22.6%, 36.5% had DM (NODAT 7.9%).
Conclusions
Prevalence of pretransplant DM and NODAT is higher in alcoholic cirrhosis and HCV. BMI has a tendency to be higher in alcoholic cirrhosis. Incidence of NODAT is lower than that described in the literature.

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Distribution of Korean obese patients based on National Health Insurance Claim Data in 2016

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South Korea has a universal health coverage system that the National Health Insurance covers approximately 98% of the overall Korean population. The claims data of HIRA contains 46 million patients per year that account for 90% of the total population in Korea and include claims from almost 80,000 healthcare service providers across South Korea as of 2011. National Health Insurance (NHI) reimbursement coverage continues to expand and there will be full reimbursement of cancer, cardiovascular, cerebrovascular and rare diseases by 2017. The proportion of GDP spent on healthcare will keep growing from the current 7.5%, driven by the ageing population. The claims data of HIRA is collected when healthcare service providers in South Korea seek reimbursements for healthcare services that the National Health Insurance Corporation agrees to cover. The annual number of Korean patients that submitted health insurance claims is approximately 46 million. The claims data of HIRA is a national data compiled from healthcare providers across the country that corresponds to the number of claims submitted by patients. In addition, the claims from patients with medical aid program, government expenditures, and veteran patients are also included in the claims data. According to the National Health Statistics 2015: National Health and Nutrition Survey, conducted by Ministry of Health and Welfare, Prevalence and trends in obesity among Korean adults were incresed since 1998. Percent of adults aged 20 years and over with obesity was 25.1% in 1998 and 39.7% in 2015.

Table 1 Annual numbers of patients.

	2011	2012	2013	2014	2015	2016
Total Patients	20,330	18,143	18,371	18,047	17,549	16,613
New Patients	16,854	14,475	14,290	13,767	13,357	12,365
Claimed Patients	3,476	3,668	4,081	4,280	4,192	4,248

Table 2 Gender distribution (2016).

Gender	Patients (*n*)	Proportion (%)
Total	16,613	100.0
Male	2,757	16.6
Female	13,856	83.4

Table 3 Age distribution (2016).

Age	Male (*n*)	Female (*n*)	Sub-total (*n*)
Total	2,759	13,898	16,657
0–9	398	524	922
10–19	638	529	1,167
20–29	340	2,281	2,621
30–39	569	4,239	4,808
40–49	448	3,689	4,137
50–59	234	2,006	2,240
60–69	93	539	632
70–79	31	81	112
Over 80s	8	10	18

*The data includes double-counted patients due to the way of age calculation in Korea.

Table 4 Distribution by clinical department (2016).

Department	Patients (*n*)	Proportion (%)
General Medicine	5,629	33.8
Internal Medicine	2,727	16.4
Pediatrics	2,424	14.6
Obstetrics-Gynecology	1,167	6.5
Korean Medicine	1,431	8.6
Family Medicine	1,084	7.0
Orthopedic Surgery	380	2.3
Others	1,809	10.9

*The data includes multiple counting among clinical departments.

Table 5 Number of inpatients and outpatients (2016).

Type	Patients(n)	Proportion(%)
Outpatients	16,521	99.9
Inpatients	10	0.1

*Spell-based proportion.

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Think insulin: a prospective study of the knowledge of insulin preparations and administration in a Cohort of nurses in district general hospital

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Introduction
Blood glucose control in insulin-dependent diabetes is heavily influenced by compliance, and how insulin is administered, which is emphasised to those with diabetes. However, when a patient is admitted to hospital, the administration of insulin is often by a nurse. The aim of this study was therefore to assess the knowledge of nurses around this subject, and to identify if there was a need for further training.
Method
We conducted a prospective audit with questionnaires, which were distributed among nursing staff from varying specialties and backgrounds, over a 40-day period in a district general hospital. 136 nurses returned their questionnaire.
Results
We found that within our cohort, more than half learnt about insulin administration from another colleague and had no formal training. The majority recognised of appropriate injection sites, however a small percentage would consider administration in the calf muscle. Around 97% of the nurses were aware

to rotate these injection sites, however awareness that areas of lipohypertrophy should be avoided for the appropriate time was answered correctly in approximately quarter of the cohort. Nearly 80% of them had knowledge about the timing that different preparations of insulin should be administered in relation to meals, however fewer percentage were not aware that the preparation before administration of insulin varies, and therefore may prepare insulin incorrectly.
Conclusion
This study suggests that whilst most areas of knowledge about insulin and insulin administration are sound, there are significant gaps, which could have adverse effects on patients. We therefore suggest that all registered nurses have adequate and continued formal education about all aspects of insulin.

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Association between NK cell activity and glucose regulation in type 2 diabetes patients

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Introduction
NK cells are cytotoxic lymphocytes critical to innate immunity. The purpose of this study is to find out the difference in NK cell activity between type 2 diabetes patients and controls, and to investigate the association between NK cell activity and glucose control.
Methods
Forty-nine subjects were enrolled in this study, with 23 type 2 diabetes patients and 26 normal glucose tolerant controls. Anthropometric and biochemical parameters were assessed. Homeostatic model assessment (HOMA) was calculated for insulin resistance. NK cell activity was measured using a newly developed NK Vue® Kit (ATgen, Seoul), which is a method of detecting and comparing interferon-gamma level from NK cells.
Results
NK cell activity was lower in type 2 diabetes patients compared to control subjects. There was a significant inverse linear relationship between NK cell activity and fasting plasma glucose after adjusting for age and gender ($r=-0.346$, $P=0.045$). Postprandial glucose and HbA1c showed a similar tendency with NK cell activity ($r=-0.313$ and -0.241, and $P=0.072$ and 0.17, respectively). Regression analysis showed HbA1c, fasting glucose and postprandial glucose to be independent predictors of NK cell activity (beta $=-0.303$, -0.360, -0.356, and $P=0.034$, 0.011, 0.033). There was no relationship between NK cell activity and HOMA-IR.
Conclusions
NK cell activity was lower in type 2 diabetes compared to controls, and it was significantly related to degree of hyperglycemia. A further, larger population study is warranted to confirm the possible correlation.

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P360

The effects of Korean red ginseng on diabetic complications and glucose modulation in type 2 diabetic patients

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Background
Korean red ginseng (KRG) has been shown to improve glucose tolerance and insulin resistance in several human studies. However, human studies on the effects of KRG on diabetic complications are lacking. We performed this study to investigate the effects of KRG administration on glucose metabolism and chronic diabetic complications in type 2 diabetes patients.
Methods
This study was a randomized, double-blind, placebo-controlled trial. 83 type 2 diabetes patients were randomly allocated to two groups assigned to consume either the placebo or KRG twice a day for 24 weeks. (taking total 2 grams a day) The primary outcomes were changes of diabetic microvascular complication markers at week 24 (serum creatinine, urinary albumin to creatinine ratio, laminin-P1 and Neurometer). The secondary outcome was change in fasting plasma glucose and HbA1c at week 24.
Results
Total of 61 patients (32 patients in the KRG group and 29 in the placebo group) completed the study. In the first 12 weeks, serum eGFR and creatinine levels deteriorated (P 0.04, P 0.01 respectively), but in the second 12 weeks, the statistically significant improvement was observed (P 0.03, P 0.01 respectively). Laminin-P1, an indicator of diabetic retinopathy, improved after 24 weeks of KRG administration but was statistically insignificant (P 0.08). At week 24, the neurometer grade was not statistically significant but showed a tendency to improve. The grade of the right arm improved from 2.38 to 1.30, the left arm from 1.81 to 0.71, the right leg from 0.99 to 0.69, and the left leg from 0.84 to 0.75 (P 0.16, P 0.12, P 0.58, P 0.86 respectively). Changes in fasting plasma glucose and HbA1c were not significant after 24 weeks of KRG administration (P 0.21, P 0.12 respectively).
Conclusions
Twenty-four week administration of Korean red ginseng in type 2 diabetic patients showed a gradual improvement in diabetic nephropathy after a transient deterioration and a tendency to improve diabetic polyneuropathy.

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P361

Phenotypic and autoimmunity analysis of patients with type 1 diabetes mellitus onset

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Introduction
Type 1 diabetes mellitus (T1DM) is considered, in general, a disease of children and young adults with normal body mass index (BMI), linked to a genetic susceptibility based on autoimmunity. However, we know that it can be diagnosed at any age and we must differentiate it from type 2 diabetes mellitus.
Objetives
To investigate the phenotypic characteristics and the presence of specific autoimmunity in T1DM patients diagnosed in our hospital.
Material and methods
We performed a descriptive observational study, including patients first diagnosed with T1DM between 2013 and 2017. They have been followed during the last year, in the Diabetes Onset clinic at Virgen de la Victoria Hospital in Málaga. We analyzed the clinical features and autoimmunity, pancreatic reserve and glicated haemoglobin (HbA1c) at onset of diabetes.
Results
We analyzed data from 69 patients with mean age 26 ($\pm$10.8 years), 61% males; IMC 23.6$\pm$3.8. 47.8% had a family history of diabetes: 24.6% T1DM and 23.2% type 2 diabetes (T2DM). Only 1.4% had autoimmune thyroid disease prior to the diagnosis of diabetes. The presentation onset of the disease was: 17.4% diagnosed casually without symptoms; 59.4% presented cardinal symptoms of diabetes; 21.7% suffered ketoacidosis and, only 7.2% required hospital admission. None of the patients died in that initial event. The autoimmunity at debut was analyzed: 47.8% had positive anti-IA2 antibodies and 92.8% positive anti-GAD antibodies. 4% had negative autoimmunity. All patients presented a decreased pancreatic reserve with C peptide values at diagnosis 1.2$\pm$0.9 ng/mL and insulin values 5$\pm$3.4 μU/mL. They had poor metabolic control (HbA1c 13.2%) that precipitated the diagnosis.
Conclusions
Nowadays we have a major difficulty to identify T1DM after 30 years due to the increasing prevalence of DM2 background. It requires the determination of autoimmunity as a useful marker to demonstrate the presence of disease. Failure to diagnose late-onset T1DM could have serious consequences due to early development of insulin dependence.

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P362

Is it useful the O'Sullivan test ≥200 to diagnose gestational diabetes mellitus (GDM)?

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Introduction
A two-step approach is usually used to diagnose GDM. At 24–28 weeks of pregnancy, a 50 g 1-hour glucose or O'Sullivan test is performed. If it is positive (≥140 mg/dl), it is followed by a 100 g-3 hours-Oral Glucose Tolerance Test (OGTT) which is considered positive if at least two or more values are ≥ of reference values (105-190-165-145 mg/dl). Despite it is not include in any clinical practice guideline, sometimes the 100 g OGTT is obviated if O'Sullivan is ≥200 mg/dl.
Objective
To evaluate the usefulness of O'Sullivan≥200 for diagnosis of GDM.
Material and methods
We analyzed data from 2774 patients presenting O'Sullivan test positive, who were carried out the 100g-OGTT at Virgen de la Victoria Hospital from 2015 to 2017 in order to compare 100g-OGTT vs O'Sullivan≥200 for diagnosis of GDM. In addition, we compared maternal and perinatal characteristics of 3 groups of patients: O'Sullivan<200 and non-pathological 100g-OGTT (A), O'Sullivan≥200 and non-pathological 100g-OGTT (B) and O'Sullivan≥200 and pathological 100g-OGTT (C).
Results
From 2774 patients with O'Sullivan test positive, 523 (18.9%) presented pathological 100g-OGTT and 2251 (81.1%) non-pathological. From 140 patients with O'Sullivan≥200, 83 (59.3%) presented pathological 100g-OGTT and 57 (40.7%) non-pathological. Therefore, the parameters of internal validity of O'Sullivan≥200 were: sensitivity 15.8%, specificity 97.4%, positive predictive value 59.2%, negative predictive value 83.3%, false-positive rate 2.5%, false-negative rate 84.1%. Comparison between groups: table 1. We only observed patients from group A to be significantly younger than those from groups B and C.

	A	B	C	*p* value
Pre-pregnancy BMI (kg/m^2)	26±5.3	26.7±5.5	27.1±5.6	0.624
Age (years)	30.8±5.6	34.1±4.5	33.3±5.5	**0.020**
Weight increase during pregnancy (kg)	7.9±5.1	11.2±6	9.1±5.9	0.310
Gestational age (weeks)	39.7±1.1	39.5±1.4	39.2±1.1	0.255
Newborn weight (gr)	3395.3±336.1	3442.9±516.3	3230.4±455.3	0.186
Type of childbirth (%)				
Eutocic	52.5	51.3	70	0.435
Instrumental	22.5	20.5	15	
Cesarean	25	28.2	15	

Conclusions
- If O'Sullivan ≥200 is considered as diagnosis of GDM, in order to avoid the 100g OGTT, 4.1 in every 10 pregnant women would be falsely diagnosed of GDM, causing unnecessary concern in patients and, probably, and an increase in GDM prevalence probably unacceptable by gestational diabetes units.
- O'Sullivan ≥200 is not useful to identify pregnant women with a higher obstetric risk.

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P363

Study on sphingolipids in tissues of animals with the diet-induced obesity

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Disturbance in insulin signaling under effect of sphingolipids is thought to be the mechanism underlying the obesity-mediated insulin resistance. The work was initiated to study sphingolipid metabolism in tissues of rats with obesity induced by a prolonged high-calorie diet. The lipid extraction and purification was performed by Folch's method; concentrations of sphingosine and ceramide were measured by Lauter *et al*. method. In obesity, the levels of total gangliosides in tissues of experimental animals were found to reduce by 16.5% and 35% in the liver and in the skeletal muscles, respectively. This was found to cause changes in cell surface properties and a decline in the glucose transport. In obesity, ratios of some ganglioside fractions were established to be abnormal, as well; thus, in particular, concentrations of GM_3 ganglioside were found to increase by 1.5 and 1.8 times in the liver and skeletal muscles of animals with diet-induced obesity, respectively. A significant increase in GM_3 in obesity could facilitate the insulin resistance onset by blocking insulin signaling on the initial stages of the hormone signal pathway. An imbalance between metabolites of sphingomyelin cycle, a decline in sphingomyelin and accumulation of sphingomyelin metabolites, such as ceramide and sphingosine, were established to take place in the liver and skeletal muscles of obese experimental animals. Ceramide/sphingosine ratios in the liver and skeletal muscles were found to be 1.17 and 1.5, respectively. This is consistent with the findings from studies on stimulation of activity of neutral sphingomyelinase, a key enzyme of sphingomyelin cycle, by 1.25 and 1.45 times in the liver and skeletal muscles, respectively. The activation of sphingomyelin cycle is thought to be an element of metabolic rearrangements in obesity. The increase in ceramide concentrations in tissues of animals with diet-induced obesity appeared to provoke the insulin resistance and type 2 diabetes mellitus onset.

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P364

Influence of HLA pattern on the age at onset of type 1 diabetes mellitus

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Aim
To determine, in type 1 diabetes mellitus (T1DM) patients, if there is any relationship between the age at onset and the number of HLA risk alleles for T1DM (DRB1*03 and DRB1*04).
Methods
Retrospective study. We selected patients with T1DM diagnosis (pancreatic autoimmunity and insulin-dependent diabetes) and age at onset >15 years, identifying 275 subjects (59.6% men and 40.4% women), with a median age at onset of 31 years (interquartile range -IQR- 13 years). We registered the following data at the time of diagnosis: presence of ketoacidosis, glycemia, HbA1c, BMI, pancreatic autoantibodies GAD, IA2 and IAA (measured by radioimmunoassay with recombinant antigen) and HLA-DRB1 typing (determined by PCR-SSO). We compared the age at diagnosis between patients with 0, 1 or 2 HLA risk alleles. Also, we compared our sample's HLA pattern with the one from a pediatric group (patients with onset before 15 years of age), obtained from a previous study from the same population and with identical diagnostic criteria *(Urrutia I, et al. (2017) Lower Frequency of HLA-DRB1 Type 1 Diabetes Risk Alleles in Pediatric Patients with MODY. PLoS ONE 12(1): e0169389).*
Results
26.7% of patients had ketoacidosis at onset. Median glycemia at diagnosis was 359 mg/dL (IQR 150), being mean HbA1c 11.95% (SD 2.52) and median BMI 22.48 kg/m^2 (IQR 4,72). 91.6% of patients had positive anti-GAD antibodies, 39.0% anti-IA2 antibodies and 29.1% anti-IAA antibodies. Median age at onset (IQR) was 31 (15) years in patients without risk alleles; 32 (13) years in patients with 1 risk allele and 27 (12) years in patients with 2 risk alleles. Statistically significant difference and decreasing trend (Kruskal-Wallis $P=0.037$; Jonckheere-Terpstra $P=0.046$). The distribution of risk alleles between the 2 groups of age was as follows, with statistically significant differences (Pearson's chi-squared test $P=0.01$).

	Number of HLA risk alleles			
Age	0 Alleles	1 Allele	2 Alleles	Total
Under 15 years	12 (7.5%)	71 (44.4%)	77 (48.1%)	160 (100%)
Over 15 years	55 (20.0%)	119 (43.3%)	101 (36.7%)	275 (100%)
Total	67 (15.4%)	190 (43.7%)	178 (40.9%)	435 (100%)

Conclusions
In type 1 diabetes patients, the presence of two HLA-DRB1 risk alleles is associated with a disease onset at a younger age.

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P365

Lipoatrophic Diabetes Mellitus: a rare special type!

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Introduction
Lipodystrophic syndromes are a heterogeneous group of congenital or acquired disorders characterized by either complete or partial lack of adipose tissue. Other prominent abnormalities of these disorders include Diabetes Mellitus and acanthosis nigricans due to the associated insulin resistance. Liver affection is common due to fatty infiltration of the liver, which can lead to cirrhosis and its complications.
Clinical case
A 31 years old single female presented to our emergency department multiple times due to hematemesis, hepatic coma and uncontrolled Diabetes Mellitus. She was diagnosed with Diabetes since the age of 15 and was on insulin therapy but always uncontrolled. She also reported history of 2ry amenorrhea. Her clinical examination revealed a BMI of 17 (normal range: 18.5–24.9), obvious loss of subcutaneous fat all over her body, pallor, acromegaloid features, acanthosis nigricans, hepatosplenomegaly, ascites and her fundus examination showed proliferative diabetic retinopathy. Her laboratory investigations showed microcytic hypochromic anemia (Hb: 11 g/dl; *n*: 12–15.5 g/dl), impaired coagulation profile (INR: 1.2; n: 1) and hypoalbumineamia (Alb: 2.4 g/dl; n: 3.5–5.5 g/dl). Her FBG was 250 mg/dl, OGTT 380 mg/dl and HbA1C 9%. Her lipid profile was normal apart from HDL of 28 mg/dl ($n > 50$ mg/dl). Liver and kidney function tests, hepatitis markers and autoimmune hepatitis markers were normal. Her TSH was normal, but her FSH was 1.4 mIU/ml (n: 1.5–9 mIU/ml), LH: 0.2 mIU/ml (*n*: 1–11.4 mIU/ml), estradiol was 20 pg/ml (n: 44–211 pg/ml). Her upper endoscopy showed grade III oesophageal varices and band ligation was done. Her Child-Pugh score was 9 (Child B).
Conclusion
Although lipodystrophy syndromes usually present with dyslipidemia, a normal lipid profile can be found in those patients with late stage disease associated liver cirrhosis. Lipodystrophy syndromes usually present early in life and the associated Diabetes Mellitus is mainly due to insulin resistance and shouldn't be misdiagnosed as T1DM. Medications such as Thiozolidines and Metformin can improve insulin resistance in the early disease before the onset of liver cirrhosis. Later on Insulin and leptin remain the only treatment lines.
Key words: Lipodystrophy, Insulin resistance, Diabetes Mellitus, fatty liver, liver cirrhosis.
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P366

Does gender-affirming hormone therapy alter insulin resistance in transgender persons?

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Background
Gender-affirming hormone therapy in transgender persons induces secondary characteristics of the experienced gender. However, androgens and estrogens are also thought to be involved in insulin sensitivity and research suggests a dose-dependent risk for developing insulin resistance when administrated in supraphysiological doses.
Aims
To assess the influence of gender-affirming hormone therapy on glucose metabolism in transgender persons.
Methods
In 90 transgender persons (35 transgender men and 55 transgender women) an OGTT was performed at baseline and one year after the introduction of gender-affirming hormone therapy as part of the ENIGI study (European Network for the Investigation of Gender Incongruence). HOMA-IR and AUC glucose during OGTT were used to quantify insulin resistance (IR).
Results
AUC glucose did not change significantly in either sex. In transgender women, we observed an increase in the median-calculated HOMA-IR, from 1.58 [1.08–1.97] to 2.06 [1.49–2.76] ($P < 0.001$) indicating higher IR after administration of estrogens and anti-androgens, an increase in total fat percentage from 18.60% ± 5.3 to 24.50% ± 10.11 ($P < 0.001$), and a decrease in the waist-to-hip ratio (WHR) from 0.87 ± 0.068 to 0.84 ± 0.084 ($P = 0.001$). In transgender men, there was no significant difference in the median-calculated HOMA-IR, but we observed a decrease in total fat percentage from 28.49% ± 5.92 at baseline to 24.30% ± 7.17 after one year ($P < 0.001$) and an increase in total activity score from 7.30 ± 2.56 to 9.05 ± 2.46 ($P < 0.001$). In transgender women, we observed a positive correlation ($R = 0.273$, $P = 0.045$) between change in WHR and change in HOMA-IR and a positive correlation ($Rs = 0.287$, $P = 0.034$) between change in HOMA-IR and change in cholesterol. In trans men, these correlations were not significant.
Conclusions
This study has identified significant changes in glucose metabolism in transgender women after one year of gender-affirming hormone therapy; IR increased, which is in line with the observed change in body composition. In transgender men, no change in IR was proven, despite a decrease in fat percentage and an increase in total activity scores.

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P367

Diagnosis and optimal medical management of patients with maternally inherited diabetes and deafness (MIDD)

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Background
Maternally inherited diabetes and deafness (MIDD) is a rare disease affecting approximately 1% of all diabetics. The most common mutation involved is a single base mutation (A-G) at position 3243 within the $tRNA^{LEU(UUR)}$ gene. The clinical characteristics normally associated with this disease include sensorineural hearing loss, macular pattern dystrophy, cardiomyopathy, and diabetes. This study aims to identify clinical phenotype and insulin secretory response to glucose.
Methods
We prospectively studied 33 patients from 23 different pedigrees with MIDD, all of which were identified from the Mater-MODY cohort database. Audiograms, ECHO's and biochemical markers including Hba1c, Lactate, Creatinine Kinase (CK) were performed. 2-hr OGTT's were performed to determine the degree of glucose tolerance, C-peptide and insulin secretory response. Clinical and metabolic data outcomes were analysed.
Results
23 (72%) patients have diabetes with 1 pre-diabetic and 9 non-diabetics. The mean age was 49.7(±12.8)y/o and BMI is 23.5(±3.2)kg/m^2. 6 (18.2%)patients were misidentified as Type 1 Diabetics while 14 (42.4%) as type 2 Diabetics. 31 patients (93.9%) had the mtDNA 3243A > G mutation. 1 had Kearns-Sayre syndrome. 1 had the m.12258C > A mutation. Heteroplasmy was determined in 24 patients (69.7%) using blood leucocytes with ranges of 3–41%. 28 patients (84.8%) were found to have sensorineural hearing loss. 8 patients (24.2%) developed cardiomyopathy. Only 1 (3.0%) patient had maculopathy and 5 patients (16.1%) developed MELAS. 8 (24.2%) patients had ophthalmopathy. 14 (42.4%) patients had 2-hr OGTT's which showed glucose (mmol/L), insulin (pmol/L) and C peptide (pmol/L) mean level at baseline/120 mins as follows: 7.8 (±4.3)/13.3 (±7.7), 63.3 (±25.8)/297.3 (±170.8), and 570.6 (±201.4)/2318.7 (±1224.8). 31 (93.9%) patients had HBa1c with mean of 66.4 (±18.6) mmol/mol. 13(39%) patients had metformin discontinued. 14(42.4%) patients are on insulin alone. 5(35.7%) are on insulin and OHA's. 4 (12.1%) are on sulphonylurea alone.
Conclusion
There is a wide phenotypic variability seen in MIDD which can lead to misdiagnosis and induction of inappropriate therapy. Patients with diabetes and

deafness should arouse suspicion of mitochondrial diabetes as well as those who are young and lean diabetics with rapid progression to insulin. These patients also have a good insulin secretory response seen on OGTT. However, 54% of patients have ended up on insulin with mean HBa1c of 66.4 mmol/mol indicating diabetic control remains brittle.

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P368

Predictors of non-alcoholic fatty liver disease in metabolic syndrome

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The results of a survey of 209 patients with Diabetes mellitus type 2 (DM 2) and 94 patients with X-syndrome were analyzed. Non-alcoholic fatty liver disease (NAFLD) is verified in 91.9% of cases with DM 2 and 83.0% with X-syndrome. Predictors that significantly influenced the development of NAFLD in X-syndrome have been identified: age (b = 0.07; Exp (b) = 1.07(1.02 ÷ 1.14); $P < 0.02$); body mass index (b = 0.37, Exp(b) = 1.45 (1.16 ÷ 1.81), $P < 0.001$), total cholesterol (b = 0.52, Exp (b) = 1.68 (1.03 ÷ 21.75), $P < 0.04$), triglycerides (b = 1.34; Exp (b) = 3.81 (1.32 ÷ 11.02); $P < 0.02$) and very low density lipoproteins b = 2.60; Exp (b) = 13.14 (1.31 ÷ 137.18), $P < 0.03$). In patients with X-syndrome over the age of 30, the relative risk of developing RR (NAFLD) = 4.00 and was statistically significant (95%CI = 1.27 ÷ 12.60). In patients with X-syndrome and BMI above 28.08 kg/m^2, the OR of the development of NAFLD – 9.54 (2.54 ÷ 35.75), with total cholesterol above 5.3 mmol/l OR – 4.08 (1.28 ÷ 13.05) The level of triglycerides is higher than 1.03 mmol/l OR – 11.37 (1.27 ÷ 12.60). If the VLDL level is above 0.47 mmol/l OR – 10.14 (1.27 ÷ 12.60). In the presence of diabetes 2, there were no significant critical values of laboratory and clinical predictors of the development of NAFLD. Therefore, patients at the time of manifestation of diabetes 2 already have severe metabolic disorders, such as NAFLD. The data cited indicate that the presence of NAFLD in the background of X-syndrome should be regarded as din from the predictors of development of diabetes 2, and the critical points of clinical and laboratory indicators, perhaps significantly below the generally accepted.

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P369

Carbohydrate metabolism indicators in athletes who stopped using anabolic androgenic steroids

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Introduction
The use of steroids for the formation of a sports figure is widespread. Anabolic androgenic steroids (AAS) are used in large doses than in therapeutic practice. Studies of the side effects of AAS on carbohydrate metabolism are hampered due to the self-over-the-counter use of AAS.
Hypothesis
We hypothesized that with the abolition of AAS, the effect of elevated doses of testosterone (Ts) and nandrolone (ND) decanoate on the utilization of glucose is reduced.
Methods
After the informational lectures among the visitors of the sports clubs of St. Petersburg on the impact of the AAS application on health, the expressed desire is included in the study. The inclusion criterion was the use of preparations of 19-nortestosterone with a course of 6 to 8 weeks in a weekly dosage of 300 to 700 mg in combination with Ts propionate and Ts enanthate, as well as the rejection of the subsequent use of anabolic steroids. BMI, HbA1c, immuno-reactive insulin (IRI) and fasting plasma glucose (FG), and HOMA-IR insulin resistance index were compared before and after 3 months after the abolition of all AAS, while maintaining the previous exercise and dietary habits.
Results
Twenty-four athletes (18M), age 27 ± 3.6 were examined. The average period of use of AAS is 7.3 weeks. After the abolition of the AAS, the IMB increased (mean difference = 4.7 kg, $P = 0.012$). The metabolism of glucose has changed in the direction of increasing all the indicators considered: FG (mean difference = 1.02 mmol/l, $P = 0.047$), IRI (mean difference = 9.83, $P = 0.023$), HOMA-IR (mean difference = 7.31, $P = 0.015$) and HbA1c (mean difference = 0.25%, $P = 0.031$). However, no violations of glucose metabolism were detected in any case.
Conclusions
The abolition of AAS in athletes caused an increase in body weight and a shift in all glucose metabolism rates closer to the upper normal values. This trend deserves further study.

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P370

Carbohydrate metabolism disorders in patients with Graves treated with systemic corticosteroid regimen

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In patients with Graves disease and Graves' orbitopathy (GO), the diagnosis was based on clinical activity score (CAS), TSH-receptor antibodies, orbital MRI assesment. Thyreometabolic status was assessed by TSH, FT4, FT3. Before the administration of high-dose intravenous glucocorticoids oral glucose tolerance test (OGTT) was performed obligatory. The patient with confirmed diabetes were excluded form the study. Acute hyperglycaemia was diagnosed at the glucose concentration ≥ 180 mg/dL, and required insulin therapy.
Results
The study group included 62 euthyroid patients with GO (85.5% women). 32 persons (51.6%) were treated with thiamazole, 16 (25.8%) after 131I, 10 (16.1%) after thyreoidectomy. Carbohydrate metabolism disorders in OGTT were found in 20 (32.2%) of the stoudy group: impaired fastig glucose (IFG) was found in 17 (27.4%); impaired glucose tolerance (IGT) in 2 (3.2%); IFG + IGT in 1 (1.6%) cases. Normal OGTT was found in 42 (67.8%) patients. A cumulative average dose of metylprednisolone was 4.5–6 g. Acute hyperglycaemia requiring insulin therapy was found in 56 (90.32%) patients, mainly at lunch and dinner time.
Conclusions
1. In euthyroid patient with Graves disease and GO disturbances in carbohydrate metabolism are more common comparing to general population.
2. OGTT should be perfomed routinely in patients with GO before systemic corticosteroid therapy.
3. Acute hyperglycaemia is observed in patient treated with systemic corticosteroid mainly at lunch and dinner time.
4. The administration of short acting insulin analogs at the meal time helps to reduce acute hyperglycaemia.

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P371

A difficult synchronous diagnosis; Type 2 Diabetes and insulinoma

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Background
In the literature there are rare cases of patients with known Type 2 Diabetes Mellitus whom are diagnosed as insulinoma. However a synchronous diagnosis with insulinoma and diabetes for a patient presenting with hypoglycemia symptoms is not an expected condition.
Case
A 79 years-old female patient was sent to our Endocrinology outpatient clinic because of repeating minor and major hypoglycemia attacks. She had no important finding in her background except a history of autoimmune thyroiditis which is held in control with levothyroxine replacement. Her renal and liver function tests were normal in her initial laboratory tests. A prolonged fasting test was performed after hospitalization. At the third hour of fasting she presented hypoglycemia symptoms and her blood sugar was found as 40 mg/dl. Blood

samples for plasma c-peptide, insulin and cortisol level measurement were obtained. Her plasma c-peptide was 3 nmol/L and plasma insulin was 101.6 μU/mL, compatible with insulinoma diagnosis while her cortisol levels were high in a manner excluding a possible adrenocortical defficiency. The patient's urine ketone was negative during this period. Urinary sulfonylurea metabolites were unmeasured because of laboratory inability for the patient who has endogenous hyperinsulinemia and hypoglycemia at the same time. A sudden spontaneous hyperglicema reaching up to 350 mg/dL was observed in the blood sugar controls while the patient was waiting for pancreatic imaging. Insulin infusion therapy was iniated to control blood sugar levels. During that stage HbA1c and anti-insulin autobodies were studied. Her HbA1c was 5.2% and her anti-insulin autoantibodies were negative. In her follow-ups; repeating hypoglycemia attacks were observed despite the interruption of insulin infusion therapy. Her control laboratory tests were again compatible with hypoglycemia accompanied by endogenous hyperinsulinemia. Her pancreas diffusion magnetic resonance imaging revealed a 12 mm hypervascular mass in the tail region suggesting a possible insulinoma. No local invasion signs were observed. After that, pancreatic mass enucleation was performed. Pathological diagnosis was insulinoma (1.1 cm, pStage I, chromogranin (+), synaptophysin (+), insulin (+), mitoses 3/10 HPF and Ki-67 index: 2%). Multiple subcutaneous insulin injection therapy was initiated after the surgical intervention because of high blood sugar results in the follow-ups. Six months after the surgery, the patient is still using basal insulin and metformin, and her last HbA1c level was 7.2%. She does not report any hypoglycemia attacks since surgery.

Conclusion

In the present case we report a rare situation in which the underlying diabetes seem to remain secret possibly because of the variable secretory pattern of insulinomas.

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P372

Immunoglobulin G4 related pancreatitis; can it be a rare cause of secondary diabetes?

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Background

Autoimmune pancreatitis (AIP) is a relatively new entity in which the exocrine pancreas shows lymphocytic infiltration. There are two subtypes of AIP; Type 1 related with Immunoglobulin G4 (IgG4) as the pancreatic manifestation of IgG4-related disease (IgG4-RD), and Type 2 related with granulocytic infiltration. The characteristic features of Type 1 AIP are increased serum IgG4 levels, lymphoplasmacytic sclerosing pancreatitis (infiltration of IgG4+ plasmacytes and lymphocytes, storiform fibrosis, and obliterative phlebitis), extra-pancreatic manifestations of IgG4-RD (e.g. sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis), and steroid responsiveness.

Case

A 60 years-old male was sent to our Endocrinology outpatient clinic because of elevated fasting blood sugar levels found during his Chest Diaseases Department follow-ups due to bronchiectasis and multiple lung cysts. His initial fasting blood glucose was 123 mg/dl. A 75-gr oral glucose tolerance test was performed and second hour glucose level was found as 246 mg/dl. Subsequent HbA1c measurement was 8.62%. In his background he had undergone lung surgery for cyst excision and tuberculosis treatment for a year. He had no first degree relative with diabetes in his family history. He had weakness, remarkable weight loss and serious postprandial dyspeptic symptoms. In his physical examination his BMİ was 22.4 kg/m^2 and no conspicuous finding except of abdominal tenderness was found. A diffusion magnetic resonance imaging of pancreas was performed according to negative family history for diabetes, weight loss and sudden presentation of diabetes in advanced age to rule out a possible pancreatic neoplasm. Pancreas MRI revealed a diffuse thickened and edematous pancreas with loss of lobulated appearance and an evident pancreatic duct. These findings were interpreted in favor of autoimmune pancreatitis. Afterwards the patient was examined for autoimmune diabetes. Anti glutamic acid decarboxylase, islet cell and insulin autoantibodies were all negative. Serum IgG4 levels were elevated (150 mg/dl), suggesting a possible IgG4-RD since the actual criteria for IgG4-RD implies a cut-off value of serum IgG4 > 135 mg/dl. We presumably thought that cystic lung disease and autoimmune pancreatitis could be manifestations of IgG4-RD and consequently IgG4 related pancreatitis can be the cause of deterioration of both exocrine and endocrine funtions of pancreas for this patient. On this basis we thought that diabetic condition of the patient could be secondary to IgG4 related AIP.

Conclusion

The concomitant onset of autoimmune pancreatitis and autoantibody positive type 1 diabetes has been described among IgG4-RD. But our case is suggesting a unique immune disturbance that compromises the pancreatic endocrine and exocrine functions.

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P373

Evaluation of glycemia correction during sleeping on the somnological indicators in type 1 diabetes patients

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Fluctuations of glycemia, the rate of glycemia decreasing, the chronic decompensation type 1 diabetes adversely influenceon diabetic complications development. Increased glycemia during sleep leads to a change in the structure of sleep and a decrease in its functions.

The aim of the study was to assess the effect of glycemic values and it's correction during sleep on somnological indicators.

Materials and methods

The study included 7 type 1 diabetes patients who received insulin therapy in a basal-bolus regime. All participants were assessed for glycated hemoglobin (HbA1c) (Architectc8000, Abbott, USA), polysomnographic study "SOMNO-lab2, Weinmann R&K" with continuous glucose monitoring (CGM) "CGMSGold" Medtronic Mini Med USA) for two diagnostic nights. CGM was performed in parallel with the PSS in the second diagnostic night.In case of detecting hyperglycemia during sleeping according to CGM (glucose level (GL) > 7.0 mmol/l) the correction of insulin therapy was performed, with repeated implementation of the complex study (PSS and CGM) with an interval of 5–7 days (Table 1). All patients were in type 1 diabetes decompensation stage (HbA1c 8.95%). Before the insulin therapy correction, fluctuations in glycemia at night were recorded in the range 8.2–13.8 mmol/l, after correction of insulin therapy - 5.50–6.50 mmol/l. Achievement of normoglycemia was accompanied by an increase in the coefficient of sleep efficiency to 86.7% vs 70.0% before correction. The duration of WASO was maximal for patients with fluctuations in glycaemia from 8.20 to 13.80 mmol/l (71 min vs 31 min). Similar results were obtained from the evaluation of the proportion of REM sleep reduction from 39.9 to 35.4%, and an increasing of N3 (2.80 vs 5.10) and N4 (1.20 vs 3.70) stages.

Conclusions

Achievement of glycemia 5.5–5.6 mmol/l for type 1 diabetes in decompension (HbA1c 8.95%) improves the structural parameters of sleep: reduces REM phase, prolongs the deep stages of slow sleep (N3, N4), and improves sleep efficiency, reduces the duration of WASO.

Table 1 Comparative characteristics of the results.

Indicator	Before correction of insulin therapy Me[25;75]	After correction of insulin therapy Me[25;75]
HbA1C (%)	8,95 [7,50;9,30]	8,95 [7,50;9,30]
The minimum glucose level during sleep (mmol/l)	8,20 [7,50;9,50]*	5,50 [5,50;6,50]
The maximum glucose level during sleep (mmol/l)	13,80 [10,50;15,00]*	6,50 [6,00;7,00]
Sleep Efficiency Ratio (%)	70,00 [69;00;73,00]*	86,70 [84,90;87,00]
WASO (wake after sleep onset)(min)	71,00 [35,00;94,00]*	31,00 [25,00;47,00]
REM (%)	39,90 [35,70;41,40]*	35,37 [24,51;37,10]
N3 (%)	2,8 [0,00;4,28]*	5,10 [3,81;6,40]
N4 (%)	1,20 [0,00;4,20]*	3,70 [2,50;4,80]

*$P < 0.05$ between groups 1 and 2.

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P374

Insulin resistance and β-cell function in patients with cystic fibrosis

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Introduction
Recent studies defend the measurements of insulin resistance and β-cell function to assess the endocrine pancreatic function in patients with cystic fibrosis (CF). HOMA-IR indexes greater than 1 translate insulin resistance and HOMA-%β values lower than 100% imply an altered β-cell function.
Aim
To describe insulin resistance and β-cell function using HOMA-IR and HOMA-%β indexes in patients with CF and compare them according to their glucose tolerance.
Methods
Observational, cross-sectional, clinical research on patients with CF evaluated at Hospital Universitario Reina Sofía (Córdoba). Statistical analysis performed with SPSS software.
Results
31 patients were included in our study. The mean age was 32.25 ± 8.89 years, with a mean CF evolution time of 23.45 ± 10.21 years. 61.3% of the patients were women. After the oral 75g-glucose test (OGTT) 13.8% patients were diagnosed with cystic-fibrosis related diabetes (CFRD), 25.1% with impaired glucose tolerance (IGT) and 51.7% showed a normal glucose tolerance. 50% of patients with IGT or CFRD had an HOMA-IR > 1 compared to the 18.2% of patients with normal tolerance who had an index greater than 1. The difference was not statistically significant ($P = 0.208$). 57.1% of patients with IGT or CFRD had an HOMA-%b $< 100\%$ in comparison to the 36.4% of patients with normal glucose tolerance who had an HOMA-%b $< 100\%$ ($P = 0.302$).
Conclusions
- In our series, half of the patients with IGT or CFRD showed abnormal insulin resistance indexes but there are not statistically significant differences with the indexes of those patients with normal glucose tolerance.
- Most of the patients (57.1%) with CF and abnormal glucose tolerance in our study presented with an impaired β-pancreatic cell function. This proportion is smaller in patient with normal glucose tolerance (36.4%) but the difference was not statistically significative.

Keywords: Diabetes, cystic fibrosis, complications.
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P375

HNF-1β maturity-onset diabetes of the young (MODY 5): defining diabetes etiology in a family with different diabetes phenotypes

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Introduction
HNF-1β maturity-onset diabetes of the young (MODY5) is uncommon, nevertheless accurate diagnosis guides individualized management and informs prognosis in probands and relatives.
Objective
To emphasize the importance of the appropriate use of clinical, biochemical and genetic investigations for the correct classification of diabetes etiology.
Case-report
A 35-year-old overweight Latin-American male was diagnosed with ketosis-prone A-β+ diabetes mellitus, however, due to a strong family history of diabetes with an autosomal dominant inheritance pattern, a niece with polycystic kidney disease during childhood, negativity for pancreatic β-Cell antibodies, and a C-peptide of 237 ng/ml, HNF-1β- MODY was suspected, further investigation revealed aplasia of the dorsal pancreas. The diagnosis was confirmed by the identification of a missense mutation (M_000458.2:c.884G>A (p.R295H) in the DNA-binding homeodomain of the HNF-1b gene (1).
Methods
Systematic clinical, biochemical characterization and HNF-1β mutational analysis were implemented to determine the diabetes etiology in four relatives.
Results
Identification of the p.R295H mutation in the proband's maternal half brother and sister confirmed the diagnosis of HNF-1β-MODY, they were previously misclassified as having type 1 and type 2 diabetes respectively. A mutation analysis of his two sons, who did not meet diabetes criteria at the time of evaluation, revealed the p.R295H mutation, a diminished glomerular filtration rate with renal cysts, and aplasia of the dorsal pancreas only in the elder son. The proband's other sister and adolescent niece had a diagnosis of diabetes mellitus and polycystic kidney disease but they were not able for testing nor his mother with diabetes but already deceased.
Conclusions
Two previously misclassified family members were shown to have HNF-1β-MODY, whereas another was shown to have clinical features associated with the mutation (pancreatic atrophy and chronic kidney failure with renal cysts) but no diabetes yet. This family exemplifies the importance of careful phenotyping and systematic evaluation of relatives after discovering monogenic diabetes in an individual since it has unique management, prognostic and genetic counseling implications.
Reference
Silva, C., Fernandez, E., Romero, J. and Martinez, G. (2017). Maturity-onset diabetes of the young type 5 (mody 5): a case report. Endocrine Abstracts.
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P376

Habitual dietary intake in response to futsal-based exercise in people with type 1 diabetes

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Background
Adequate and appropriate nutrition in type 1 diabetic athletes is essential not only to increase the physical performance but also to prevent the hypoglycemic events. Detailed nutrition history represents the initial step in developing a proper meal plan according to the specific characteristics of the physical activity performed.
Purpose
This study assessed changes in habitual dietary intake and macronutrient distribution in response to intermittent-type futsal-based exercise under free-living conditions in people with type 1 diabetes who have not previously received structured nutritional diabetes education.
Methods
Nine people with type 1 diabetes (HbA_{1c} $7.6 \pm 0.9\%$; Age 28 ± 5 years; BMI 23.7 ± 1.8 kg/m^2; Diabetes duration 11.3 ± 6.4 years) completed a 24-hour weighed food diary on two separate occasions: 1) on a day containing exercise (EX), and 2) a non-exercise day (CON). The exercise day consisted of performing a standardized 80-minute intermittent-type typical futsal-based training session. All participants were competing at an international-level in futsal. Participants had not previously received dietary education as part of their diabetes care. Food frequency and dietary intake were subsequently analyzed.
Results
EX resulted in 78% of participants experiencing hypoglycemia, whereas this was limited to 45% under CON. Meal frequency and meal-time energy intake was similar between conditions ($P \geq 0.050$), however all participants under EX consumed additional carbohydrate-based snacks, whereas this was limited to 56% under CON. Correspondingly, total kcal intake was on average 31% greater under EX (EX 2470 ± 783 vs. CON 1888 ± 601 kcal.day^{-1}; $P = 0.047$), with more carbohydrate (EX 287.7 ± 81.5 vs. CON 238.4 ± 92.6 g.day^{-1}; $P = 0.044$), fat (EX 94.6 ± 50.3 vs. CON 60.9 ± 22.0 g.day^{-1}; $P = 0.013$), and protein (EX 128.2 ± 68.2g vs. CON 99.2 ± 44.2 g.day^{-1}; $P = 0.039$) consumed.
Discussion
This is the first investigation to show that people with type 1 diabetes with no prior structured nutritional diabetes education performing intermittent-type futsal-based exercise rely predominantly on carbohydrate-based snacks to prevent exercise-induced hypoglycemia rather than adjust meal frequency, meal-macronutrient distribution, or meal-macronutrient amount.

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P377

TWEAK levels in patients with prediabetes and diabetes mellitus

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Introduction
Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) belongs to TNF family and is released from inflammatory cells. It has been reported that TWEAK has several biological actions ranging from cell proliferation to stimulation of apoptosis. In *in vitro* studies, it was reported that TWEAK has alleviating effect on insulin resistance in hepatocytes. TWEAK decreases insulin resistance induced by TNF-a through activation of phosphatase 2A pathway in adipocytes. In our study, the relationship between TWEAK levels and biochemical parameters was assessed in patients with prediabetes and diabetes mellitus.
Material and method
The study recruited overall 90 patients including 32 patients with diabetes mellitus (17 men, 15 women), 32 patients with prediabetes (14 men, 18 women) and 26 controls (12 men, 14 women). The diagnosis of prediabetes was made according to fasting blood glucose measurement (100–126 mg/dl) and 75-gr OGTT (2 h glucose: 140–199). Diabetes group included patients with newly diagnosed type II diabetes mellitus. Biochemical evaluations were performed in all patients. Homeostasis Model Assessment (HOMA) was calculated by using following formula: HOMA-IR = Fasting Blood Glucose (mg/dl) × Fasting Insulin (uIU/ml)/405. Spearman's correlation analysis was used to assess correlations.
Findings
There were significant differences in TWEAK among three groups ($P = 0.001$). There was no significant difference between prediabetes and diabetes groups ($P = 0.867$) while there was significant difference in controls when compared to prediabetes or diabetes groups ($P = 0.001$).
Discussion
In our study, the finding presence of significant difference between controls and prediabetes or diabetes groups but not between prediabetes and diabetes groups suggests that TWEAK levels can be affected even at early phase of insulin resistance. The negative correlation between TWEAK and insulin resistance or inflammation markers may be a clue indicating that TWEAK levels can be used as a novel, early marker for metabolic syndrome. The decreased TWEAK levels by increasing insulin resistance and inflammation raises the likelihood of using TWEAK as an early marker for metabolic syndrome which is now considered as a common public health issue.

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P378

Description of clinical, biochemical and radiological variability of Hepatocyte Nuclear Factor-1βeta (HNF1β) Mutations

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Background
HNF1β mutations are one of the commonly identified genetic causes of renal malformations, but one of the less common forms of MODY. HNF1β is involved in the development of kidneys, liver, pancreas, intestine and urogenital tract. Patients can present with distinctive but highly variable clinical features. The aim of this study is to evaluate the clinical, biochemical and radiological variability of HNF1β variants and the challenge of management on the basis of the insulin secretory response to glucose.
Methods
11 HNF1β mutation positive subjects underwent phenotyping with a 2-h OGTT to determine their degree of glucose tolerance and insulin secretory response. Biochemical testing included magnesium, urate, faecal elastase (FE). Abdominal and pelvic ultrasound (US), Magnetic Resonance Imaging (MRI) of pancreas and liver were performed.
Results
Diabetes was present 9/11 patients. Diabetes was diagnosed at 29 ± 16 years of age, BMI 23.4 ± 2.5 kg/m^2, mean HbA1c was 67 ± 15 mmol/mol. 5/9 on insulin (MDI) and 3/9 started on oral hypoglycaemic agents (OHAs-Metformin and Gliclazide MR) after OGTT and HNF1β mutation positive, with a significant reduction of insulin doses. 2/9 on OHAs required basal insulin after 10 years of diabetes diagnosis, 1/9 on OHA and 1/9 diet controlled. The insulin secretory response to glucose was variable but present in all the patients. Glucose (mmol/l), Insulin (mU/l) and C-Peptide (μg/l) mean at 0 min/120 min: 9.3(±4.8)/19.3(±8.3), 56.2(±65.8)/150.0(±77.3), 363.7(±219.5)/1364.6(±1031.7) respectively. 6/11 had mild asymptomatic hypomagnesaemia 0.64 ± 0.09 mmol/l. 3/11 had hyperuricemia and 2 had early onset gout. 5/11 had deranged LFT's. 3/11 had sub-clinical pancreas exocrine insufficiency (FE 52 ± 40 μg/g). 7 patients have undergone for MRI demonstrating pancreas malformation in 4 subjects (atrophic pancreas, agenesis of the body and tail, partial pancreatic divisum), female genital tract abnormalities in 2 cases (uterus didelphys) and one patient with seminal vesical cysts as part of infertility investigation. 5/11 had renal cysts. 1 patient with CKD stage 3. 7 different mutations were identified; p.Gly83Ser (p.G83S) has been described as a novel mutation.
Conclusion
This case series highlights the spectrum of clinical manifestations of HNF1β variants. Genetic diagnosis enables the physician to screen for hypomagnesaemia, gout, pancreatic insufficiency and pancreatic/hepatic/genital malformations. The patients could benefit from insulin and/or OHA for treatment on the basis of insulin secretory response.

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P379

Maternally inherited diabetes and deafness (MIDD): the many faces of the same disease in a Spanish family

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Introduction
Maternally inherited diabetes and deafness (MIDD), is a rare entity. Most commonly, it is related to a point mutation in the mitochondrial DNA (mtDNA) at position 3243 (m.3243A > G) encoding the gene for tRNA. A high index of suspicion is required for the diagnosis due to a wide heterogeneity in its clinical presentation which reflects different levels of mutated mtDNA among mitochondria in a given tissue (heteroplasmy). Thyroid cancer risk has never been specifically assessed in this population.
Case-report
We report a 39-year-old male diagnosed with type 2 diabetes mellitus (T2DM) at the age of 29 when he presented with polyuria. His body mass index at diagnosis was 22.6 kg/m^2 and pancreatic autoimmunity was negative. After the presumed T2DM diagnosis he was started on oral hypoglycemic agents. He was added on insulin after 4 years of diagnosis because of poor glycemic control. He had never experienced any episodes of diabetic ketoacidosis (DKA). He had a subcapsular cataract of the left eye but there was no evidence of retinopathy, neuropathy, kidney disease, muscular weakness or cardiac disease at the time of presentation. His past medical history included a sensorineural hearing loss at 25 years of age. His family history revealed a bilateral hearing loss at the age of 50 in his mother who had also been diagnosed with T2DM and multinodular goiter in the last year. His sister was diagnosed with type 1 diabetes mellitus when she was 15 years of age and on physical examination she also had a multinodular goiter. The patient, his mother and sister underwent genetic testing which confirmed the m.3243A > G mutation with a level of heteroplasmy of 90%, 61% and 5% respectively. During the follow up the patient showed a thyroid papillary microcarcinoma with BRAF-V600E-K mutation. He was referred for thyroidectomy.
Conclusions
This family exemplifies the clinical heterogeneity of MIDD linked to the degree of heteroplasmy in the mitochondria of affected tissues. Probands commonly show high levels of heteroplasmy, they prompt the diagnosis as they are usually the most affected members of their families. Careful phenotyping and systematic evaluation of relatives after the diagnosis of the index case is mandatory due to unique management, prognostic and genetic counseling issues. The distribution of thyroid disease and thyroid cancer risk in this population is elusive. To our current knowledge this is the first reported case of MIDD and concurrent differentiated thyroid carcinoma.

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P380

The detection of disordered eating risk in patients with type 2 diabetes mellitus

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Background and aims
Type 2 diabetes is strongly associated with obesity as the major potentially modifiable risk factor. Apart from total caloric intake, certain eating patterns have been associated with the risk of diabetes and insulinoresistance. Researchers have found that specific groups in the community may be at increased risk of eating disorders, including people with diabetes and those who are obese. The aim of the study was to detect the risk of disordered eating in patients with T2DM using EAT-26 questionnaire.
Materials and methods
We studied 107 patients with type 2 diabetes mellitus (20 men and 87 women) recruited from clinical and community settings. The mean age of the participants was 61.75 + 9.32 years; the mean BMI was 34.39 + 6.72 kg/m^2. The most widely used standardized measure of eating disorders symptoms the Eating Attitudes Test (EAT-26) was used for the purposes of the present study. Questions are scored on a Likert scale from 0 (never, seldom, or sometimes) to 3 (always). A score greater than 20 represents a risk for developing a eating disorder, and participants are categorised as being at risk of disordered eating.
Results
The analysis showed that 49 patients with T2DM (45,7%) have score more than 20 on EAT-26; 58 patients (54, 37%) scored less than 20. Among the subgroup of men the value 20 and more was revealed in 7 questionnaires (35%), the score less 20 – in 13 ones (65%). In the subgroup of women 42 females (48,7%) were 'positive' on their cut-offs, 45 females (51,3%) account less 20. The significantly higher mean value (2,01) was received on the question 'I avoid foods with sugar in them': 52 persons (48,6%) answered 'always', 26 persons – 'usually', 9 persons (8.4%) – 'often', 20 persons (18.7%) – 'never, seldom, or sometimes'. The higher rate on this question maybe associated with the specifity of diabetes and could influence the total score rate on the scale. Future research efforts are required to strengthen the present findings.
Conclusion
Our findings showed a high risk of disordered eating among patients with T2DM according to EAT-26 questionnaire. More research is needed to understand the role of eating disorders in T2DM.

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P381

Gestational diabetes and weight gain in outpatient practice

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Hyperglycaemia is one of the most common medical conditions women encounter during pregnancy. The occurrence of gestational diabetes mellitus (GDM) is rising and it represents an important modifiable risk factor for adverse pregnancy outcomes. Similar to GDM, excessive weight gain is associated with a number of undesirable consequences for both the mother and neonate. The aim of this study was to evaluate prevalence of GDM in outpatient practice and investigate associations between glucose metabolism and gestational weight gain (GWG) during pregnancy.
Methods
We analysed retrospective data of all adult pregnant women who were followed up in Vilnius Karoliniskiu clinic, Lithuania and gave birth in 2016. GDM was diagnosed using the UK National Institute for Health Care Excellence (NICE) criteria. GWG was categorized as low, appropriate and excessive according to Institute of Medicine Guidelines.
Results
Data of 415 women were analysed. Mean age at delivery was 30.14 ± 5.13 years. The first antenatal visit was at 11.64 ± 4.47 gestational week. Oral glucose tolerance test was performed at 26.62 ± 4.14 gestational week. A total of 86 women (21%) were diagnosed with GDM and 4 (1%) had overt diabetes in pregnancy. 15.1% of women having GDM were normal weight, 33.3% – overweight, 51.6% – obese. Overweight and obese women had 3.68 (95% CI 2.21–6.11) times higher odds ratio for developing GDM comparing with underweight or normal weight women ($P < 0.0001$). Mean total GWG was higher in underweight and normal weight women group than that in overweight and obese women group (13.87 ± 4.85 vs 11.59 ± 5.88 kg ($P = 0.001$)). Mean total GWG was higher in normal glucose tolerance group compared to GDM group (13.73 ± 4.84 vs 12.15 ± 6.09 kg ($P = 0.03$)). Excessive GWG have had one-third (33.1%) of all women. Excessive GWG was more frequent in GDM group than in healthy women (45.9% vs 30.1%, $P = 0.009$).
Conclusions
This audit presents a relatively high prevalence of GDM in everyday outpatient practice. Overweight and obesity significantly increases risk of GDM. Compliance with lifestyle guidelines helps women with GDM to control weight gain during pregnancy, nevertheless excessive gestational weight gain is still more frequent in women with GDM.

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P382

Oral glucose tolerance test in reclassification of gestational diabetes after delivery – results from portuguese national registry

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Introduction
Gestational diabetes (DG) is associated with higher risk of diabetes mellitus (DM), and it's recommended to perform an oral glucose tolerance test (OGTT) with 75 g after delivery to its reclassification. However, not all scientific societies recommend it.
Aim
To evaluate glucose tolerance with OGTT after delivery in women with DG and the risk factors to glucose intolerance in glycaemia at 120′.
Methods
Retrospective cohort study that included women with DG who performed OGTT after deliver between 2012 and 2015, from national register of diabetes and pregnancy of Portuguese Society of Diabetes. The WHO diagnostic criteria were considered.
Results
7435 women were included: 92.2% ($n = 6857$) had a normal response; 0.8% ($n = 60$) presented DM criteria (43% ($n = 26$) at 0' and 57% ($n = 34$) at 120′), 1.1% ($n = 84$) had impaired fasting glucose (IFG) and 5.9% ($n = 434$) had impaired glucose tolerance (IGT). Women with DM criteria at reclassification presented higher values at fasting glycaemia (FG) in 1st trimester (119.7 ± 35.0 vs 97.3 ± 7.1 mg/dl; $P < 0.001$), at glycaemia at 60′ at OGTT in 2nd trimester (211.3 ± 42.3 vs 175.5 ± 30.1 mg/dl; $P < 0.001$), daily dose of insulin (31.4 ± 20.5 vs 21.7 ± 16.9 U; $P < 0.001$) and $n°$ of injections (2.9 ± 1.6 vs 2.2 ± 1.3; $P < 0.001$), and earlier diagnosis (16.4 ± 8.4 vs 19.7 ± 8.5weeks; $P = 0.004$) and delivery (37.5 ± 2.2 vs 38.4 ± 1.6; $P < 0.001$). Of 32 women with FG in 1st trimester ≥126 mg/dl, 34.4% had DM criteria, 18.8% IFG and 12.5% IGT at reclassification. At reclassification, women with DM criteria at 120′, were associated with IFG after delivery (OR = 24.17; IC95% 11.32–51.60), insulin therapy (OR = 7.40; IC95% 3.14–17.44), DG diagnosis at 60′ in 2nd trimester OGTT (OR = 3.85; IC 95% 1.30–11.40), newborn large for gestational age (LGA) (OR = 3.20; IC95% 1.59–6.46) and DG in previous pregnancy (OR = 2.59; IC95% 1.36–4.95). Women with IGT were associated with these risk factors and also age ≥35years (OR = 1.54; IC 95% 1.27–1.87).
Conclusion
The prevalence of glucose intolerance after delivery was 7.8%, with the majority of women (5.9%) being diagnosed with IGT, a condition with increased cardiovascular risk. DM was diagnosed in 0.8% of women, exclusively by glycaemia at 120′ in 57%. DM diagnosis at 120′ was associated with DG in previous pregnancy, DG diagnosis at 60′ in 2nd trimester OGTT, insulin therapy during pregnancy, newborn LGA and IFG after delivery. These data reinforces the importance of OGTT for correct reclassification of DG, with increased relevance in women with risk factors.

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P383

Relationship between circulating 25-hydroxyvitamin D and glucose homeostasis in women with postmenopausal osteoporosis

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Context
Postmenopausal osteoporosis (PMO) is associated with other comorbidities such as cardiovascular disease and impaired glucose homeostasis. Vitamin D insufficiency is highly prevalent, and may be a common link between these disorders. Recently, it has been shown that vitamin D may be involved in insulin resistance; however, this relationship has not been well evaluated in women with PMO.
Objective
To assess the relationship between circulating levels of 25-hydroxyvitamin D (25OHD) with parameters of glucose homeostasis in a cohort of women with PMO. Additionally, the threshold of 25OHD serum concentration was determined, from which influence at glucose homeostasis were observed in our study population.
Design and methods
Cross sectional study including 40 non obese women with PMO belonging to the coverage area of San Cecilio University Hospital in Granada (Spain). Clinical, anthropometric, bone mineral density and, biochemical parameters related to glucose metabolism (HbA1c, insulin, glucose homeostasis model [HOMA2-Calculator]) and mineral metabolism (25OHD, infracarboxylated osteocalcin [ucOC]) were determined. A descriptive analysis and a multiple linear regression analysis (significance <0.10) was performed.
Results
Mean values of the characteristics of the study population: age 62 ± 8.5 years; BMI 25.4 ± 3.9 kg/m^2; percentage of body fat (PBF) 33.9 ± 6.9%; lumbar spine T-score -2.9 ± 0.6 SD; femoral neck T-score -1.8 ± 0.7 S.D.; 25OHD 42.9 ± 19.8 ng/dl; HbA1c 5.4 ± 0.3%; ucOC 8.3 ± 10 ng/ml. Circulating levels of 25OHD were related to glucose metabolism parameters: negatively with HOMA2-IR ($R=-0.314$, $P=0.07$), HOMA2-%B ($R=-0.468$, $P=0.003$) and insulin levels ($R=-0.332$, $P=0.06$); and positively with HOMA2-%S ($R=0.368$, $P=0.02$); resulting in an indicator of insulin resistance independently of age, BMI, PBF and ucOC. The patients with serum 25OHD ≥45 ng/ml showed lower values on HOMA2-IR and HOMA2-%B indexes, lower insulinemia, and greater HOMA2-%S index.
Conclusions
Our results support the hypothesis that circulating 25OHD levels are related to glucose homeostasis and therefore constitute a modifiable cardiovascular risk factor in women with PMO.

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P384

Demographic and clinical factors associated with having ischemic heart disease as a multiple contributing causes of death among diabetes mellitus deaths in the United States and Brazil

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Introduction
Between-country comparability and validity of mortality statistics is a global public health challenge, especially for cause-of-death assignment of diabetes mellitus (here after diabetes) in relation to cardiovascular disease. The multiple contributing causes of death (MCD) representing comorbidity are not used to classify mortality cause, as the underlying cause of death (UCD) becomes the cause-of-death. Diabetes increases risk of ischemic heart disease (IHD). To aid in policy making for preventing IHD deaths as comorbidity of diabetes, this study determines demographic and clinical factors on having IHD as a MCD among deaths with diabetes as the UCD.
Methods
Death records including causes of death were obtained through the World Health Organization, which are originally from the Centers for Disease Control and Prevention (CDC) in the US for years 2012–2015, and from Sistema de Informação sobre Mortalidade in Brazil for years 2006-2009 and 2011-2013. A logistic regression analysis was conducted to identify factors associated with having IHD as a MCD among diabetes deaths.
Results
IHD appeared as the MCD in 38% and 16% of 305,885 deaths in the U.S and 367,717 deaths in Brazil that were deaths with diabetes as the UCD, respectively. Marital status, smoking, age, place of death, high cholesterol, and existence of autopsy were significantly associated to having IHD as a MCD in the two countries. In the U.S., in addition, race was significantly associated to having IHD as a MCD. In Brazil, significant factors also included assistance of medical staff, education, having hypertension, and obesity (P-values <0.05).
Conclusion
MCD could play a large role in better characterizing diabetes mortality estimates. Differences in existence of IHD as comorbidity of diabetes deaths were observed between the U.S. and Brazil. Factors identified in this study could help detect population subgroups with masked IHD among diabetes deaths. Representation of IHD comorbidity among diabetes deaths is needed for adequate public health measures to be taken, leading to lower mortality through a more target-specific intervention for non-communicable disease.

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P385

Gestational diabetes – association of lipid profile in pregnancy with post-partum dysglycemia

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Introduction
Lipid profile characterization in women with gestational diabetes mellitus (GDM) and its impact on post-partum dysglycemia remains to elucidate. The aim of this study was to evaluate lipid profile in women with GDM during pregnancy and 8 weeks after and to study its correlation with glycemic control.
Methods
This study was carried out in a central hospital in Portugal. All women with GDM diagnosed from January/2014 to December/2015 were enrolled. A lipid profile was recorded during pregnancy and at post-partum reclassification and was later accessed. GDM diagnosis was made through fasting glucose or through OGTT glucose accordingly to international guidelines (IADPSG consensus panel, 2010).
Results
We included 448 women, mean age 33.49 ± 5.0 years, mean pre-pregnancy weight 68.61 ± 14.7 kg, mean BMI 26.35 ± 5.6 kg/m^2 and mean pregnancy weight gain 8.73 ± 5.5 kg. Post-partum, there was a statistically significant decrease of total (254.12 ± 50.7 vs 189.16 ± 36.4), LDL (LDL-c) (157.39 ± 44.6 vs 115.97 ± 33.3) and HDL (HDL-c) (67.52 ± 5.2 vs 55.12 ± 12.9) cholesterol and triglycerides (195.79 ± 62.1 vs 83.73 ± 46.9). In respect to lipid profile at pregnancy, we found a statistically significant correlation between c-HDL and OGTT glucose at 60′ ($r=-0.175$) and 120′ ($r=-0.343$) and between triglycerides and OGTT glucose at 120′ ($r=0.164$). In respect to post-partum, we found a statistically significant correlation between total and LDL-c and pre-pregnancy weight ($r=0.143$. $r=0.154$, respectively). LDL-c was also found to have a statistically significant correlation with OGTT glucose at 120′ ($r=0.178$), while HDL-c was found to have a statistically significant correlation with fasting glucose at the diagnosis ($r=-0.184$). Triglycerides presented a statistically significant correlation with fasting glucose at diagnosis ($r=0.460$) and with glucose at 120′ in the reclassification test ($r=0.169$).
Conclusion
There is a close relation between lipid and glycemic profile in women with GDM. Elevated glucose levels at the diagnosis of GDM seem to correlate with lower HDL-c and higher triglycerides in the post-partum period. Elevated 3rd trimester triglycerides correlate with a higher glucose levels at reclassification test, thus maternal hypertriglyceridemia during pregnancy can negatively influence glycemic control in the post-partum period.

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P386

Changes in the glutathione system in patients with impaired carbohydrate metabolism

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Introduction
Many studies have found that markers of oxidative stress (OS) are significantly increased in diabetes mellitus, but only a limited number of studies describe the disturbance of OS in pre-diabetes.
Objective
To study the state of the glutathione system in patients with disorders of carbohydrate metabolism and concomitant diseases of the cardiovascular system (CVS).
Materials and methods
181 patients were included under the age of 55 years: group 1–27 patients with newly diagnosed pre-diabetes without concomitant CVS diseases, group 2–28 patients with newly diagnosed pre-diabetes and the presence of concomitant IHD, group 3–20 patients with newly diagnosed pre-diabetes and the presence of concomitant IHD and peripheral vessels atherosclerosis, group 4–47 patients with type 2 diabetes (T2D), group 5–59 practically healthy persons. The total glutathione (GSHt) and glutathione in the oxidized form (GSSG) contained in the erythrocytes were measured by a glutathione reductase reaction. The redox potential of glutathione (Eh) of erythrocytes was determined by the Nernst equation.
Results
In group 1 GSHt and GSH were significantly lower, compared with group 3 ($p_{1\text{-}3}=0.012$, $p_{1\text{-}3}=0.053$, respectively). When compared with the group group 4, a significantly higher GSH content was detected ($p_{1\text{-}4}=0.068$). In the group 4 there was a significant decrease in GSH and 2GSH + GSSG, and an increase in GSSG, compared to group 2, group 3 and group 5 ($p_{4\text{-}2}=0.006$, $p_{4\text{-}3}=0.006$, $p_{4\text{-}5}=0.003$, $p_{4\text{-}2}=0.005$, $p_{4\text{-}3}=0.009$, $p_{4\text{-}5}=0.014$, respectively, and $p_{4\text{-}2}=0.005$, $p_{4\text{-}3}=0.016$, $p_{4\text{-}5}=0.001$, respectively). According to the results of the study, the highest concentration of glutathione (5.11 [1.98, 5.78]) was in the group 2. The presence of concomitant IHD decreases the ability of glutathione to recover, as evidenced by the significantly lower values of GSH and GSHt in group 4, compared to group 1 ($p_{4\text{-}1}=0.004$, $p_{4\text{-}1}=0.016$, respectively), and an increase GSSG ($p_{4\text{-}1}=0.004$). Eh was significantly higher in group 4 than in groups of 1,2,5 ($p_{4\text{-}1}=0.035$, $p_{4\text{-}2}=0.013$, and $p_{4\text{-}5}=0.055$).
The conclusion
The state of the glutathione system can be considered as one of the markers of vascular lesion in patients with prediabetes. At the stage of pre-diabetes, the patient rarely has complaints typical of cardiovascular diseases. However, at this stage, the mechanisms that lead to the development of complications in the subsequent already type 2 diabetes mellitus begin to form.

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P387

The effect of the dopamine agonist cabergoline on insulin sensitivity in the skeletal muscle: an *in vitro* study in a mouse cell model demonstrating mediation by serotoninergic receptors

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Insulin resistance (IR), characterized by an impairment of target tissues to insulin responsiveness, is the core defect preceding diabetes. Preclinical and clinical data have suggested a role for the dopaminergic system in glucose homeostasis control. The aim of the current study was to investigate the role of the dopamine agonist cabergoline (CAB), displaying high affinity for dopamine type 2 (DR2) receptor and low affinity for serotonin receptors (5-HTRs), in the regulation of muscle IR. An *in vitro* model of mouse skeletal muscle (C2C12) has been used in baseline and IR palmitate (1 mM for 16 h)-induced conditions. DRs and 5-HTRs messenger and protein levels have been evaluated by RT-qPCR and WB, respectively. DR2 protein expression has been analyzed also through liquid chromatography tandem-mass spectrometry (LC-MS/MS). The effect of escalating doses of CAB (10^{-10} M, 10^{-8} M, 10^{-6} M) alone or combined with $2*10^{-8}$M insulin on glucose uptake (GU) was evaluated by a colorimetric assay, while intracellular signaling has been investigated by WB. To evaluate GLUTs translocation, membrane proteins have been isolated from cytoplasmic proteins and analyzed by WB. As revealed by RT-qPCR and WB, C2C12 did not express DRs but expressed messenger and protein levels of 5-HT2RA and B. LC-MS/MS confirmed the complete absence of D2 protein. In C2C12 at baseline condition, the percentage (%) of GU was significantly stimulated by 10^{-10} M and 10^{-8} M CAB, either alone or combined with insulin. A significant increase of IRS-1 Tyr608 and Akt Ser473 phosphorylation levels as well as membrane GLUT4 translocation were shown after the 10^{-8} M CAB combined with insulin exposure, suggesting that CAB might stimulate GU by activating insulin receptor (INS-R) signaling. In condition of IR, C2C12 exposed to 10^{-6} M CAB with insulin showed a significant increase of % GU as well as GLUT1 membrane translocation after 10^{-6} M CAB alone. Moreover, 10^{-6} M CAB either alone or combined with insulin triggered a significant increase of pAMPK Thr172 and a significant decrease of pERK Thr202/Tyr204, suggesting that in IR state, CAB might stimulate glucose internalization through AMPK pathway independently from INS-R signaling activation. Pre-treatment with 5-HT2RA (altanserin) and 5-HT2RB (Ly272015) antagonists inhibited CAB-regulated intracellular signaling and GU suggesting that CAB acts through 5-HTRs. In conclusion, these data show that CAB induces muscle GU both at baseline and IR conditions by improving insulin and AMPK pathways respectively, through the serotoninergic pathway.

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Eating habits, food choices and physical activity in adult patients with type 1 diabetes mellitus

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Introduction
Eating habits, food choices and exercise affect glycaemic control in patients with Type 1 Diabetes Mellitus (T1DM). The purpose of this study was to evaluate eating behaviors, food choices and the level of physical activity in patients with T1DM.
Methods/design
A random sample of 84 patients (M/F: 31/53) with T1DM, aged 34 + 11.9 years, living in central Greece, were individually interviewed. Food consumption was assessed by a semi-quantitative food-frequency questionnaire and adherence to the Mediterranean diet (MedDiet) was evaluated using the KIDMED questionnaire. Physical activity also assessed by validated questionnaires. Information was collected regarding self-perceived body size, dietary knowledge, control for eating, meal and snack frequency and eating out of home. Height, weight, BMI and waist circumference (WC) were also measured. Glycemic control was assessed by glycated hemoglobin.
Results
Mean BMI was 24.5 + 5.3 kg/m^2 and about half patients (48.9%) were overweight or obese (BMI >25 kg/m^2). Mean WC was 92.7 + 11.2 cm (M: 98.5 + 12.2 cm and F: 89 + 9.2 cm) and HbA1c was 7.7 + 1.7%. Body image concerns, education about food, personal control for eating and the presence of diabetes are factors found to affect food choices. Regular meals at home were frequent, 75% reported to have breakfast daily, 58% have a midmorning snack, 99% eat lunch and dinner daily and 46.4% have a snack before bed. Eating out with friends and/or family and eating at work was related to higher consumption of 'junk type of food'. Only 33.3% of patients reported high adherence to MedDiet (KIDMED index >8), 54.8% reported moderate (KIDMED index 4–7) and 11.9% reported low (KIDMED index ≤ 3) adherence to MedDiet. 13.1% of patients reported a high physical activity level and 22.6% reported moderate levels at least three times per week. The great majority (64.3%) of patients had low levels or no regular physical activity. No correlation was found between HbA1c levels and adherence to MedDiet ($r=0.432$, $P=0.298$). HbA1c levels were negatively correlated with the level of physical activity ($r=-0.233$, $P=0.00$).
Conclusion
The presence of diabetes, personal issues, peers and family affect food choices in patients with T1DM. As physical activity remains low and the prevalence of obesity is increasing in this group of patients, implementation of multilevel strategies is necessary for improving glycaemic control and avoiding weight gain.

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Preconception management in type 2 diabetes mellitus (T2DM): there is still much work to do

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Background
Preconception planning is essential for a successful pregnancy in women with pregestational diabetes,although many women still do not plan their pregnancies. The rapid outbreak of T2DM among the general population, including women of childbearing age, is one of the largest public health issues. The aim of this study is to describe time trends in preconception planning, obstetric and perinatal outcomesduring the past 8 years in ourpregestational care unit, focusing on T2DM.
Material and methods
We performed a retrospective case study of all deliveries of pregnant T2DM or T1DM women followed in our unit from 2009 to 2016 ($n=114$). Wedescribed clinical data, preconception care, pregnancy and neonatal outcomes, comparing the results: 1) among T1DM ($n=68$) and T2DM ($n=46$) and 2) T2DM pregnancies between different periods of time (2009–2012 vs. 2013–2016). We analyzeddata, evaluating differences using χ^2 test, Student' *t*-test or Mann–Whitney test.
Results
As compared with T1DM pregnant, T2DM pregnant wereolder (age: 33.9 ± 4.9 vs. 31.0 ± 4.5 years [mean ± S.D.]; *P* 0.002) and had less duration of diabetes (2 (1–5) vs. 14 (6–20.8) years [median (P25–P75)]; *P* 0.000). T2DM had less preconception care (15.2 vs 54.4%; *P* 0.000) and higher parity (nulliparous: 15.2 vs 42.6%; *P*0.002). 40% of T2DM pregnantwere obese (17.9% of T1DM; *P* 0.01) but had less total pregnancy weight gain (4.9 (2.6–10.1) vs. 11.2 (5.1–14.3) kg; *P* 0.001). No differences between HbA1c levels at pregnancy diagnosis (6.7% (6.1–7.4)) or during 1rst trimester (6.5% (6.0–7.2)) were detected, butduring 2nd and 3rd trimester T2DM were more likely to achieve lower glucose levels (HbA1c: 5.7%(5.6–6.1) and 5.9% (5.6–6.2) vs. 6.2% (5.8–6.5) and 6.3% (5.9–6.5);*P* 0.000 and *P* 0.001). There were no differences in obstetric and perinatal outcomes between T1DM and T2DM (risk of preeclampsia (PE): 8.8%, preterm delivery: 16.7%, cesarean section: 45.6%, newbornlarge for gestational age: 33.3%, neonatal hypoglycemia: 23%, congenital malformations: 20.2%, newborn's admission to intensive care unit (ICU): 24.8%, perinatal mortality: 1.8%). Between 2013 and 2016, compared to the preceding 4 years, T2DM had more total pregnancy weight gain (7.2 (4.3–10.7) vs 2.9(1.3–5.1) kg; *P* 0.008) and a tendency of less pregnancy preparation (8.3 vs 22.7%; *P* 0.175). There was less proportion of PE (2.2 vs 15.6%; *P* 0.016) and less neonatal hypoglycemia (2.2% vs 15.6%; *P* 0.016) with no statistically significant differences in other outcomes, although a trend towards improvement was detected regarding preterm birth (8.3% vs 22.7%), c-section (25% vs 50%), newborn's admission to ICU (13% vs 22.7%), and malformations (12.5% vs 18.2%).
Conclusion
Risk of pregnancy outcomes in T2DM pregnant are as high as in T1DM. Lately only 8.3% of T2DM had preconception management. It is crucial to enhance the need for pre-pregnancy preparation in this group to improve health outcomes.

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Kinky and sparse hair as an associated finding inmaternally inherited diabetes and deafness

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Background
Maternally inherited diabetes and deafness (MIDD) is a rare form of diabetes due to defects in mitochondrial DNA (mtDNA). Maternal transmission of diabetes and neurosensorial deafness are the main clinical features of MIDD followed by other mitochondrial disorders, myopathies, and macular dystrophy. 3243 A > G is the mutation most frequently associated with this condition, but also other mtDNA variants have been linked with MIDD. We describe the case presenting with hyperglycemia and hair findings diagnosed as MIDD.
Case report
A 9-year-old boy was referred to our clinic for hyperglycemia. He was the third child of consanguineous healthy parents. He had previously diagnosed bilateral neurosensorial deafness and he was wearing a conventional hearing aid. His weight was 24 kg (3–10.p), height 132 cm (50.p), and BMI 13.8 kg/m^2. He had kinky, sparse, and ivory hairs. Fundus examination was normal, maculopathy was not detected. There was no hepatomegaly or splenomegaly. On laboratory; his glycated hemoglobin (HbA1c) was 6.6%, hemogram, thyroid, hepatic and renal function tests were normal. Celiac and diabetes-related (islet cell antibody, anti-glutamate decarboxylase, insulin auto antibody) antibodies were negative. Serum copper and zinc levels were normal. Electromyogram was normal. The whole mtDNA analysis was revealed TRNL1 gene the mutation.
Conclusions
Determination of the mitochondrial origin of diabetes is important for genetic counseling and clinical care. The whole mtDNA should be screened because the 3243A > G variant is not as frequent in children as in adults for MIDD our patient's hair features was suspected Menkes Kinky hair disease and zinc deficiency. The brittle, tangled, sparse, steely or kinky hairs that are often white, ivory, or gray in color with easy pluckability are main findings for Menkes Kinky hair disease is an X-linked recessive trait caused by mutations in the ATP7A gene leading to disturbed copper metabolism. However, our patient's serum copper and zinc levels were normal.

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Stiff - person syndrome in an old woman with late onset type 1 diabetes mellitus

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Introduction
Stiff person syndrome (SPS) is a rare neurological disease resulting in stiffness and spasm of muscles and, as a consequence, severely impaired ambulation. Pathophysiology of the disease is based on an increased muscle activity caused by the decreased level of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) due to an autoimmune attack against glutamic acid decarboxylase (GAD); enzyme which is also one of the main autoantigens of type 1 diabetes mellitus (DM). SPS is often associated with autoimmune disorders and it may rarely occur as a paraneoplastic syndrome. We present a singular case of SPS in a woman with late onset type 1 DM.
Case report
A 74 years old woman had been recently diagnosed with type 2 diabetes due to a mild hyperglycemia. Treatment with metformin was started but few months later she developed polyuria, polydipsia and weight loss (BMI 24.5 kg/m^2). She was referred to our center and insulin therapy was initiated as well as autoimmunity study was requested. Blood test showed anti GAD level of 3701.9 U/ml (normal range: 0–3.9) with a very low C peptide (0.21 ng/ml, normal range: 0.9–4) so, she was diagnosed with type 1 DM. Two years later she presented with progressive gait disturbance and rigidity of lower limbs. Neurological examination revealed dystonia and tremors in lower extremities as well as areflexia in both Achilles tendons. Routine laboratory tests including complete blood count, chemistry profile, creatinine kinase, C-reactive protein and thyroid function were in the normal range. Brain and cervical spine MRIs were unremarkable but electromyography (EMG) observed continuous motor unit discharge and simultaneous co-contraction in lower extremities. SPS diagnostic was made based on the clinical findings, EMG results and a positive therapeutic response to diazepam. Treatment with benzodiazepines, gabapentin, intravenous immunoglobulin and mycophenolate was started with significant improvement observed in the follow-up.

Conclusions
SPS is a rare condition but it should be considered in any patient with bizarre gait disorder and autoimmune disease, especially type 1 DM, in order to prevent delay in diagnosis and long-term neurologic disability.

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Autoimmune hypoglycemia in a patient with slow type 1 diabetes

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Introduction
Hypoglycemia is rarely due to an auto-immune etiology, which is the presence in the serum of the patient of anti-insulin or anti-insulin receptor antibodies. The present case is of a slow type 1 diabetic patient in whom the autoimmune origin of repeated hypoglycemia was found.
Case
A 58 years old female patient, Who is a slow type 1 diabetes carrier, and has been on premixed human insulin for 4 years, the patient presented repeated episodes of hypoglycemia: both nocturnal and late postprandial. She also denied skipping meals or having any drug intake that is likely to cause hypoglycemia, the search for signs in favor of gastroparesis was negative, and no family history of Autoimmune disease was found. Physical Examination revealed a conscious patient, glucose blood level was 0,6 g/l, No lipodystrophy was found. Blood tests showed normal liver and kidney function, Cortisol level at 8 AM was 15 µg / dl; after stimulation (Synacthen test): 26 µg / dl, Anti-transglutaminase IgA antibody detection was negative with absence of IgA deficiency), High levels of anti-insulin antibodies was discovered; it returned higher than 50 IU/ml, The diagnosis of autoimmune hypoglycemia was confirmed by the high level of the Anti-insulin antibodies. The indication for corticosteroid therapy was made alongside the use of the insulin analogue.
Conclusion
Autoimmune hypoglycemia is considered a rare etiology of hypoglycemia, human insulin remains as an immunogenic product that induces the secretion of specific antibodies, especially among patients with autoimmune diseases.

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Insulin resistance in diabetes mellitus type 1, and its association with cardiovascular disease, sex hormones

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Objective
The aim of the study was to determine frequency of insulin resistance, in individuals with type 1 diabetes mellitus and the link between insulin resistance and cardiovascular disease, sex hormones. The task of the research is to determine the frequency of insulin resistance among people with diabetes mellitus type 1. To determine association between eGDR and age, sex, cardiovascular disease, chronic complications of diabetes and sex hormones. To determine association between insulin resistance and duration of disease, body mass index, chronic complications of diabetes mellitus. To determine eGDR cutoff value when chronic complications of diabetes are more frequent. To find the association between insulin resistance and cardiovascular disease among people with diabetes mellitus type 1.
Research design and methods
The study is a part of an international research 'Litdiane'. The study involved 200 people, with type 1 diabetes mellitus, over the age of 18 years. With reference to survey and information from medical records, performed the data analysis. Insulin resistance is associated with eGDR. It was calculated by the following formula eGDR = 24.31- 2.22(LKS)-3.29 (AH)-0.57 (HbA1c%). Estimated glucose disposal rate was divided into tertiles. One – way ANOVA were used to contrast means between eGDR groups. To determine the influence of factors multinomial logistic regression method was applied. The data was considered statistically significant at $P < 0.05$.
Results
Cutoff value of eGDR which shows resistance of insulin is <6.4 mg/kg/min. When eGDR is <6.4 mg/kg/min, diabetic complications were more common. eGDR is statistically significantly lower for patients with chronic complications of diabetes mellitus ($P < 0.001$), and for patients with cardiovascular diseases (5.5 ± 2.4 mg/kg/min ($P < 0.001$)). eGDR has the highest influence on cardiovascular diseases occurrence ($P = 0.004$). SHBG concentration is positively associated with higher eGDR. Testosterone levels are related with resistance of insulin in type 1 diabetes patients.
Conclusions
Diabetic complications are more common when eGDR is <6.4 mg/kg/min. Insulin resistance was found for 33.5% of patients. The resistance of insulin is statistically significantly associated with micro- and macro-vascular complications. Insulin resistance statistically significantly affects progression of cardiovascular disease. Smoking, male gender, low testosterone level, duration of disease were associated with resistance of insulin.

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Mitochondrial diabetes in 40 patients belonging to 30 Tunisian families: phenotypic and genotypic heterogeneity

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Introduction
Mitochondrial diabetes (MD) is characterized by a broad spectrum of phenotypic and genotypic involvement. Through a cohort study of 40 patients with DM, we tried to correlate this diversity of phenotypic expression with the biomolecular substratum of the mitochondrial genome in the Tunisian population.
Results
Epidemiologically and anthropometrically, our series fits the literature data with age at 31.6 years (5–52), female predominance (82.5%) and normal BMI in 60% of cases. Diabetes was MIDD2 in ¾ cases, with a significantly higher incidence of diabetic retinopathy 42.5% versus 8-13% in the literature. Regarding the extra-pancreatic manifestations, reticular macular dystrophy, very characteristic of DM, was absent in all our patients; as well as retinitis pigmentosa (15% of cases versus 57–86%). Perceptive deafness, classically almost constant, was only present in half of the cases. A dilated cardiomyopathy was found in only 1 case versus 18 to 34% in the literature. The biomolecular study of the mitochondrial genome revealed the absence of the most frequently described mutation associated with DM: m.3243A > G (tRNA Leu). This led us to look for the mutation m.14709T > C (tRNA Glu), found in 6 patients belonging to three different families, however the study of the heteroplasmic rate in 2 families did not reveal a correlation with the spectrum of phenotypic involvement. In addition, sequencing of the entire mitochondrial genome has revealed other polymorphisms not described in the literature and having a key role in the functioning of the mitochondrial respiratory chain.
Conclusion
Our cohort is characterized by a phenotypic and genotypic heterogeneity. It seems that the m.3243A > G mutation is not specific to our Tunisian population and that the m.14709T > C mutation was more frequent. A larger scale study is needed to determine the impact of heteroplasmic rate on the spectrum of phenotypic involvement.

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P395

Hyperandrogenaemia in women with type 1 diabetes mellitus; associations with lipids and lipoprotein particle size, and early vascular disease

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Hyperandrogenaemia and polycystic ovary syndrome (PCOS) are common in women with Type 1 diabetes, but it is not known if they contribute to increased cardiovascular risk. We aimed to compare associations between androgen levels, lipid variables and early atherosclerosis in reproductive-age women with and without T1DM. 87 (16 with PCOS) women with T1DM (mean $\pm$ SD; age 28.7 $\pm$ 6.1yrs, BMI 25.4 $\pm$ 4.4kg/m^2), and 87 (16 PCOS) nondiabetic women (mean $\pm$ SD; age 31.8 $\pm$ 5.9yrs, BMI 28.3 $\pm$ 4.01kg/m^2), were studied. Androgens (LCMS), plasma lipids and lipoprotein subclasses (polyacrylamide-gel-tube-electrophoresis) and carotid-intima-media-thickness (CIMT), a validated marker of atherosclerosis were measured. In non-diabetic women SHBG correlated negatively and free testosterone positively with VLDL($r=-0.37$/$r=0.32$), triglyceride (TG) ($r=-0.26$/$r=0.28$) and TG/HDL-C ratio($r=-0.28$/$r=0.29$) while DHEAS correlated negatively with LDL-C($r=-0.29$) ($P<0.05$ for all). In T1DM, SHBG correlated negatively($r=-0.26$) and free testosterone positively($r=0.22$) with TG and TG/HDL-C ratio($r=0.24$) while androstenedione correlated positively with TC($r=0.24$), VLDL ($r=0.32$) and LDL-C($r=0.32$) ($P<0.05$ for all). TC, LDL-C and TG were not associated with CIMT in either group, but VLDL($r=0.59$, $P<0.0001$) and the proportion of atherogenic small-dense LDL (sdLDL, $r=0.24$, $P=0.04$) correlated with CIMT only in women with T1DM. Androgens did not correlate with CIMT in either group. In summary, in T1DM and nondiabetic women, SHBG and free testosterone correlated with lipid and inflammatory markers characteristic of insulin resistance, but did not correlate with CIMT. VLDL and sdLDL were associated with CIMT in T1DM only. These results do not support a role of hyperandrogenaemia in atherogenesis in T1DM. The role of VLDL and sdLDL in early atherogenesis in T1DM requires further exploration.

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P396

Association of the FTO gene rs9939609 polymorphism with carbohydrate metabolism disorders in the Republic of Tatarstan

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Aim
To investigate the possible association of the FTO gene rs9939609 polymorphism with different disorders of carbohydrate metabolism in residents of the Republic of Tatarstan.
Materials and methods
A total of 237 patients with a single history of hyperglycemia were examined. They underwent an oral glucose tolerance test on a BS-200E Mindray analyzer. 198 patients from the whole cohort had various disorders of carbohydrate metabolism, so they were included in the study. The patients were divided into several groups: 110 people with type 2 diabetes mellitus (DM2), 46 with hyperinsulinism, 29 with impaired glucose tolerance, and 13 with impaired fasting glycemia. DNA was isolated from whole blood, followed by analysis of gene polymorphisms with real time polymerase chain reaction (TestGen). The distribution of patient's genotypes and alleles was compared with the control group consisting of residents of the Republic of Tatarstan without carbohydrate metabolism disorders ($n=851$).
Results
The frequency of alleles and distribution of genotypes of the A/T polymorphism of the FTO gene in the control and study groups corresponded to the Hardy-Weinberg distribution ($\chi^2=1.13$, $P=0.29$ and $\chi^2=0.72$, $P=0.4$, respectively). The distribution of genotypes (AA - 33%, AT - 50%, TT - 17%) and alleles (A - 58%, T - 42%) in individuals with DM2 significantly differed from the control group (AA - 14%, AT - 44.5%, TT - 41.5%, A allele - 36.3%, T allele - 63.8%, OR = 2.38, $p<0.0001$). Significant differences from controls have also been noticed in distribution of genotypes of patients with other disorders of carbohydrate metabolism: with hyperinsulinism (AA - 47.8%, AT - 34.8%, TT - 17.4%, A allele - 65.2%, T allele - 34.8%, OR = 3.3, $P<0.0001$); with impaired glucose tolerance (AA - 55.2%, AT - 34.5%, TT - 10.3%, A allele - 72.4%, T allele - 27.6% OR = 4.62, $P<0.0001$); with impaired fasting glycemia (AA - 30.8%, AT - 53.9%, TT - 15.4%, A allele - 57.7%, T allele - 42.3%, OR = 2.38, $P=0.04$).
Conclusion
The association of the FTO gene with the risk of developing DM2 in Republic of Tatarstan has been proved, which is also confirmed by the results of other studies. The positive correlation of the FTO gene A allele with early carbohydrate metabolism disorders was revealed, which allows to identify groups of increased risk for violations of carbohydrate metabolism. Apparently, the A/T polymorphism of the FTO gene is mostly associated with the secretory function of pancreatic beta cells.

Keywords: FTO, gene, diabetes mellitus type 2, impaired glucose tolerance
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Reactive hypoglycaemia – a debilitating condition

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Although there are no formal diagnostic criteria, reactive hypoglycaemia is a term generally used to describe hypoglycaemia occurring within a few hours after meal intake where other causes of hypoglycaemia such as medications, cortisol deficiency and insulinoma have been excluded. Although this is considered a benign, easily managed condition here we present three cases of reactive hypoglycaemia with significant debilitating symptoms. The first case is a 26-year-old man who was referred to the Endocrine clinic following an episode of complete loss of consciousness after two pints of beer and another episode where he was found to be unrousable in the morning with a capillary blood glucose of 3.1mmol/l. He described a history of one stone weight loss over six months alongside symptoms of headache, dizziness, nausea and lethargy occurring 2–5 h after meals. An oral glucose tolerance test arranged by the general practitioner found capillary blood glucose of 2.7 mmol/l at 2 h. Subsequent extended oral glucose tolerance test over 5 h revealed symptomatic hypoglycaemia with serum glucose levels as low as 1.6 mmol/l at 2.5 h. The second case is a 58-year-old lady referred after having a pre-syncopal episode while driving and was found to have a capillary blood glucose of 3.0mmol/l in the Emergency Department. She also described episodes of feeling unsteady on her feet and her legs giving way associated with a craving for sweet foods a few hours after oral intake. There was nothing of note on her past medical history. She experienced symptomatic hypoglycaemia with a serum glucose of 3.9 mmol/l at 3 h following extended oral glucose tolerance test. The third case is a 44-year-old lady who presented with symptoms of dizziness and unsteadiness on her feet occurring around 3.5 h after eating lunch which resolved after having a sugary drink or food. Following an extended oral glucose tolerance test she experienced moderate hypoglycaemia with serum glucose of 2.3 mmol/l at 3 h with sweatiness and light-headedness.
Conclusion
The above three cases highlight the significant morbidity and potentially severe symptomatology associated with reactive hypoglycaemia. This should be considered in patients presenting with multiple symptomatology in particular syncope and pre-syncope following a meal as awareness of the same enables us to manage and control reactive hypoglycaemia by less but more frequent intake of a balanced diet.

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P398

Abstract withdrawn.

P399

Metabolic syndrome in patients with latent autoimmune diabetes of adults (LADA)

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Introduction
Latent autoimmune diabetes in adults (LADA) is an endocrine disorder characterized by a progressive destruction of pancreatic beta cells by an autoimmune mechanism leading to absolute insulin deficiency. However, recent studies have shown the presence of a certain degree of insulin resistance in LADA patients, hence the possibility of the existence of a metabolic syndrome in these patients. The purpose of our work is to evaluate the presence of metabolic syndrome among our LADA patients.
Patients and methods
Our study has included 27 patients followed for LADA. Anthropometric measures, measurement of blood pressure and lipid status were ordered in all patients. Metabolic syndrome was diagnosed on IDF criteria.
Results
The mean age of patients was 47.6 years and the mean age of discovery was 39.7 years. The sex ratio was 1.4 with a female predominance. 50% of our patients have normal BMI, 15.3% are thin, 15.3% are overweight and 19.2% are obese. Waist circumference was pathological in 57% of patients and 19.2% had hypertension. Hypertriglyceridemia was present in 14.8% of patients and hypo HDLemia in 22.2%. Metabolic syndrome was found in 22.2% of patients according to WHO or IDF criteria.
Conclusion
Our study showed that LADA patients may have a metabolic syndrome, and that the presence of the latter does not exclude the diagnosis of LADA. One could also think of the benefit of insulin sensitizers in the management of LADA diabetes.

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P400

Gestational diabetes and postpartum follow up

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Introduction
Gestational diabetes mellitus (GDM) is an important public health issue because of its frequency and its risk of progression to T2DM. Risk of subsequent type 2 diabetes is associated with quality screening and to certain risk factors.
Objective
The aim of our study was to assess the evolving risk of GDM to type 2 diabetes, and to find its significant predictive factors.
Methods
We report a retrospective study from January 2016, aboutpatients followed at the Ibn Rochd University Hospital of Casablanca's Endocrinology – Diabetology department for gestational diabetes. The parameters studied were age, GDM's recurrence, family history of diabetes, pre-gestational BMI, pregnancy term at GDM's discovery, initial fasting glucose, treatment adopted, taking weight during pregnancy, delay of postpartum screening, and means of screening. Statistical analysis was univariate for all the variables using SPSS version 22.0.0.
Results
Mean age of our patients was 32.4 ± 6.5 years. Two thirds of the patients were between the ages of 30 and 40. The average gestational diabetes' term diagnostic was 20.2 ± 0.45 weeks of gestation. Family history of Diabetes was found in 68% of cases. During pregnancy, insulin therapy was required in 59% of the patients. Screening for dysglycemia was 1.5 to 16 months post-partum (average 6 months). An OGTT 75g was made in 47 patients (62.7%). In contrast, 9.3% of the study population benefited only from fasting blood glucose and HbA1c. We noted that 21% were lost to follow-up. Type 2 diabetes was diagnosed in 22 patients (25.5%), moderate fasting hyperglycemia in 8 patients (9.5%), carbohydrate intolerance in 12 patients (14%). The only factor significantly associated with development of diabetes has been the use of insulin during pregnancy ($P=0.02$). The FPG and HbA1c initially high were frequently associated, without having a significant impact.
Discussion
Consistent with the literature, our results reflected a high incidence of postpartum dysglycemia in our population, hence the importance of an initial awareness and extended follow-up, with a particular attention for use of insulin during pregnancy.

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P401

Glycemic variability and diabetes-related antibodies titer at diagnose in type 1 diabetic patients: is there a correlation?

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Introduction
Type 1 Diabetes (DM1) is associated with a destructive autoimmune process of pancreatic b-cells. The presence of anti-islet cells (ICA) antibodies (Ab), as well as for distinctive antigens – GAD65, IA2 or Insulin (IAA) - is related to the disease development.
Aim
To evaluate the effect of DM1 antibodies on the measures of glycemic variability (GV) obtain through continuous glucose monitoring (CGM).
Materials and methods
Were included 41 patients with DM1 who performed CGM, corresponding to 7872 h of CGM. Analytic and clinical data were obtained through patient's individual process and hospital's electronic process consultation. Data from the CGM was obtained using iPro2 Medtronic®. Statistical analysis was performed on SPSS Statistics v.25®. We included as measures of GV: Mean Tissue Glucose, Standard-Deviation (SD), *CONGA, LI, JINDEX, LBGI, HBGI, GRADE, MODD, MAGE, ADDR, M-value* e *MAG*.
Results
Patients were stratified in two groups (1: patients with £2 different classes of positive Ab ($n=28$) *vs* 2: patients with >2 different classes of positive Ab ($n=13$)). We found significant differences between groups regarding disease duration 17.03 ± 8.6 vs. 14.15 ± 8.9; $P=0.004$), age (32.39 ± 10.6 vs. 25.15 ± 7.17; $P=0.000$) and HbA1c (7.93 ± 0.93 vs. 7.58 ± 1.02; $P=0.013$) at the MCG date. Concerning different measures of GV, we also found significant differences related to mean tissue glucose (8.88 ± 2.3 vs. 8.23 ± 2.2; $P=0.021$), *CONGA* (7.68 ± 2.2 vs 7.13 ± 2.1; $P=0.036$), JINDEX (48.78 ± 23.2 vs 43.42 ± 24.5; $P=0.02$), HBGI (10.44 ± 6.6 vs 8.97 ± 6.5; $P=0.037$), GRADE (8.05 ± 4.7 vs 6.89 ± 4.5; $P=0.042$), MODD (4.01 ± 1.1 vs 3.41 ± 1.1; $P<0.001$) and ADDR (30.22 ± 9.8 vs. 26.02 ± 10.5; $P=0.006$). We established a significant correlation between Ab anti-GAD65 ($r_s=-0.137$; $P=0.031$) and Ab anti-IA2 ($r_s=0.23$; $P=0.017$) and GRADE measure. When the model was adjusted for potential confounding variables, namely disease duration, we still observed an inverse correlation between variability and presence of Ab and ADDR measure ($P=0.003$).
Conclusions
In our sample, we found significant differences between the number of Abs and several measures of GV (Mean, *CONGA, JINDEX, HBGI, GRADE, MODD, ADDR*). However, after adjusting the data for the duration of disease, only the differences on ADDR were still observed, highlighting the importance of the clinical data and disease evolution for the interpretation of GV.

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P402

Major adverse cardiovascular events and in-hospital outcomes in patients with diabetes

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Background
Diabetes is an important risk factor for major adverse cardiovascular events (MACE). Although the increased risk for MACE is well known, the impact on the in-hospital outcomes remains incompletely understood. Our aim was to evaluate the interrelation between diabetes and MACE in a central hospital in the North of Portugal between 2009 and 2015.
Methods
We evaluated retrospectively the hospitalizations due to MACE including stroke or transient ischemic attack (TIA), acute coronary syndrome (ACS) and heart failure from the Hospital Coding Centre. We have studied the distribution by age, sex, causes and duration of admissions. Statistical analysis was performed with Student's *t*-test and chi-squared test. A two-tailed P value <0.05 was considered significant.
Results
A total of 124150 hospitalizations were registered during the studied period, with a total of 13425 MACE. The proportion of MACE admissions among all admissions was significantly higher in patients with diabetes (13.4% vs 9.7%, $P<0.001$). Patients with diabetes presented a higher proportion of stroke or TIA (3.9% vs 3.5%, $P<0.001$), acute coronary syndrome (5.3% vs 3.8%, $P<0.001$) and heart failure (4.2% vs 2.4%, $P<0.001$) compared with patients without diabetes. Among individuals with MACE, the group with diabetes was older (71.6 ± 10.8 vs 69.4 ± 15.3 years, $P<0.001$) and presented a higher proportion of women (46.0% vs 41.6%, $P<0.001$). There were no significant differences regarding in-hospital mortality among patients with diabetes compared with patients without diabetes (5.4% vs 5.3%, $P=0.737$). On the other hand, patients with diabetes presented a longer duration of MACE hospitalization (9.9 ± 9.6 vs 8.8 ± 8.5 days, $P<0.001$).
Conclusions
We observed a higher proportion of admissions for MACE among patients with diabetes. Furthermore, a longer duration of MACE hospitalization was observed among patients with diabetes. The higher incidence of MACE in patients with diabetes highlight the importance of improving the prevention and treatment of cardiovascular complications in this population.

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P403

Screening for autoimmune endocrinopathiesAt 300 insulin-dependent diabetics type1

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Introduction
Type 1 diabetes is an autoimmune disease that can be associated with other autoimmune endocrinopathies. Occurrence of these autoimmune endocrinopathies increases the management of diabetes and affects the quality of life of patients. The aim of our study was to clarify the prevalence of endocrine autoimmune diseases associated with diabetes type 1 and their clinical characteristics.
Patients and methods
A descriptive analytical and retrospective study was conducted in Endocrinology, Diabetes and Metabolism Department, Ibn Rochd University Hospital of Casablanca, extended over a period of 7 years (January 2007 - December 2016) including 300 T1Ds. All patients had benefited from thyroid hormone assessment; 104 patients, had benefited from early morning cortisol assessment. Statistical analysis was univariate for all the variables using SPSS version 22.0.0
Result
We found 32 patients (10.66%), including 28 women and 4 men, of mean age 28.6 years (15-53 years) had a polyendocrinopathy, type T1D-hypothyroidism in 12 patients, T1D-hyperthyroidism in 11 patients, T1D- adrenal insufficiency (AI) in 5 patients, T1D-AI-hypothyroidism in 3 patients, and T1D-AI-hypoparathyroidism in one patient. Weight loss motivated the thyroid hormones assessment in 76% of cases, hypoglycemia in 62%, palpable thyroid in 37%, and palpitation in 28%. Hypoglycemia's motived the early morning cortisol assessmentin 98% of the cases, asthenia in 82%, and Weight loss in 77% and the melanodermia in 20%. Diabetes preceded endocrinopathy in 18 patients, with a difference in age of 3 years 3 months. Endocrinopathy preceded diabetes in 6 patients; with a difference of 3 years 9 monthsand they were concomitant in 8 patients. Anti-TPO ABs was positive in 12 patients, anti-TSH receptors in 09 patients and anti-21 hydroxylases in 4 patients.
Conclusion
The thyropathies are the most autoimmune endocrinopathies associated with T1D, essentially in young women. Timing and circumstances of discovery are variable, hence the importance of regular biological testing.

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Diabetes complications

P404

Mortality related to diabetes in orthopedic surgery patients

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Introduction
Episodes of poorly controlled diabetes (DM) are one of the most frequent medical complications during hospitalization in the elderly population.
Goals
To analyze the mortality rate (M) in patients with DM who undergo some medical decompensation during an admission to Orthopedic Surgery and Traumatology (OST).
Material and methods
Descriptive analysis of patients admitted to OST who suffered some type of medical decompensation that needed to notify an team of Internal Medicine, Endocrinology and Cardiology. We analyze the patients with known DM and their M.
Results
From June 2008 to December 2014, 1486 consultations were sent to Internal Medicine, Cardiology, Nephrology and Endocrinology regarding patients admitted to the OST area who had undergone some type of medical decompensation during admission. Of these patients, 437 (29.4%) had a documented history of DM. Their M was 11.21% (49 patients), with the M of the decompensated 10.3%.
Conclusions
DM is a cause of medical decompensation in 8.3% of patients admitted to OST. One in four known diabetics had abnormal blood glucose levels. Patients with a history of DM, decompensated or not, present a slightly higher M than the global number of decompensated patients in this area. We suggest that an early evaluation of blood glucose levels by Cardiology, Nephrology, Endocrinology or Internal Medicine could be beneficial in terms of morbidity and mortality.

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Mortality related to diabetes in vascular surgery patients

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Introduction
Episodes of poorly controlled diabetes (DM) are one of the most frequent medical complications during hospitalization in the elderly population.

Goals
To analyze the mortality rate (M) in patients with DM who undergo some medical decompensation during admission to Vascular Surgery and Angiology (VS).
Material and methods
Descriptive analysis of patients admitted to VS who suffered some type of medical decompensation that needed to notify a team of Internal Medicine, Endocrinology and Cardiology. We analyze the patients with known DM and their M.
Results
From February 2011 to December 2014, 173 consultations for Internal Medicine, Endocrinology, Nephrology or Cardiology were carried out regarding patients admitted to the VS area who had suffered any medical decompensation during admission. Of these patients, 94 (49.1%) had a documented history of DM. Its M was 23.4% (22 patients), with the M of the decompensated patients being 16.76%.
Conclusions
DM is a single cause of medical decompensation in 4.6% of patients admitted to the VS. However, associated with decompensation of other vascular risk factors, one out of four known diabetics had abnormal blood glucose levels. Patients with a history of DM, decompensated or not, present a M that is much higher than the overall M of decompensated patients in this area. We suggest that an early assessment of glycemia and strict monitoring of diabetic patients suffering from some medical decompensation in VS, by Cardiology, Nephrology, Endocrinology or Internal Medicine could be beneficial in terms of morbidity and mortality.

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P406

Diabetes and other frequent clinical problems in patients admitted in orthopaedic surgery

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Objectives
To analyze the most frequent consultations on patients admitted to Orthopedic Surgery and Traumatology (OST) unit asked to medical physicians.
Material and methods
Descriptive analysis of consultations on patients admitted to OST who suffered any medical decompensation that needed to be notified.
Results
From June 2008 to November 2014, 1486 consultations were sent from OST to a medical team (Internal Medicine + Cardiology + Endocrinology + Pneumology + Nephrology) assigned to control of medical pathologies in surgical areas. The most common consultations were: dyspnea 371 (25%), pluripathology control 163 (11%), diabetes control 124 (8.3%) and high blood pressure 123 (8.3%). Digestive pathology was 10.5% (specified according to the disease: diarrhea, nausea-vomiting or abdominal pain). Analytic alterations 4%. Dyspnea was analized as it was considered too nonspecific. 48.7% were of respiratory origin: pneumonia (32%, of which 56% nosocomial), noncondensing respiratory infection (26%), exacerbation of COPD (18%), bronchospasm (16%) and pulmonary thromboembolism (2%). 41% of dyspnea had a cardiological origin; 66% the main factor inducing heart failure was not clearly identified; 13.6% presented excessive intravenous fluid therapy, 11.3% anemia secondary to the intervention, 11.3% uncontrolled atrial fibrillation. Then anxiety (4.7%). In 3,7% no dyspnea was observed. The reason for consultation was poorly controlled DM in 124 patients (8.3%), with 111 patients (89.5%) presenting hyperglycemia and 13 (10.5%) presenting hypoglycaemia. However, since the consultations were made by the Orthopedic Surgeon who requested it, after the initial evaluation of all these patients, the diagnosis of poorly controlled DM was only considered in 108 patients (7.4% of the total decompensated patients), since the rest, despite presenting glycemia above 125 on fasting, were considered controlled taking into account their particular clinical situation. This implies an actual decompensation of 24.7% of patients with known DM.
Conclusions
25% of consultations for medical decompensation in OST patients correspond to dyspnea, almost half from respiratory origin and somewhat less from cardiological. An important percentage are due to intrahospital processes (nosocomial pneumonia and excessive intravenous therapy). DM is a cause of medical decompensation in 7.4% of patients admitted to OST. One in four known diabetics had abnormal blood glucose levels. An early examination of patients with personal history of medical problems such as diabetes, performed before the surgery, could be beneficial in terms of morbidity.

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P407

A novel lipid tetrad index as predictor of premature coronary artery disease in diabetic patients

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Background
The prevalence of premature coronary artery disease (CAD) has increased steadily in diabetic patients in the recent years. The aim of this study was to explore if evaluation of lipid risk factors like Lipoprotein(a) [Lp(a)] and conventional lipid profile parameters can be a efficient predictor of the cardiovascular risk in the patients of Diabetes.
Methods
Sixty individuals with angiographically proven premature CAD and 30 healthy individuals matched for age & sex were studied a tertiary health care center, New Delhi,India, over a period of 18 months. CAD patients were divided into two groups based on presence ($n=30$) [Group I] and absence ($n=30$) [group II] of type 2 diabetes mellitus (DM). The serum levels of Lipoprotein(a) were measured by ELISA and routine lipid profile (serum triglyceride, total cholesterol, HDL-C and LDL-C) was measured by automated analyzer. Angiographic clinical vessel scoring was also done for all the patients.
Results
Lipoprotein (a) levels for Group I was 40.26 ± 8.23 mg/dl, Group II was 40.81 ± 11.16 mg/dl respectively which was significantly (i.e. $P<0.01$) higher than the levels in healthy controls[Lp(a) $= 16.39 \pm 5.71$ mg/dl]. We found a significant increase in mean levels of Total cholesterol (TC), Low Density Lipoprotein-Cholesterol (LDL-C) and Triglyceride (TG) in cases than controls($P<0.01$). In contrast High Density Lipoprotein-Cholesterol (HDL-C) values decreased. Non HDL-C was calculated using the equation = [Total Cholesterol(TC) - LDL-C]. Lipid Tetrad Index (LTI) and Atherogenic Index were also calculated for all patients. LTI was calculated using the equations LTI = [total cholesterol x triglycerides x lipoprotein(a) / HDL-C] and the Modified Lipid Tetrad Index that we propose was calculated using the equation MLTI = [non HDL-C x triglycerides x lipoprotein(a) / HDL-C]. On analyzing by cumulative probability plot the new modified Lipid Tetrad Index defined by us is able to discriminate case and control populations more precisely than the existing LTI and Atherogenic Index. The Modified Lipid Tetrad Index has a better sensitivity and specificity than the existing LTI and also has a better correlation with the angiographic vessel score in all patients.
Conclusion
The new proposed Modified Lipid Tetrad Index is a better indicator of premature CAD diabetic patients from India, than the exsisting Lipid Tetrad Index and Atherogenic Index. The new proposed Modified Lipid Tetrad Index appears to be a predictor of the severity of premature CAD in diabetes patients.

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Oral health care behaviors among Tunisian patients with diabetes mellitus.

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Aim
The aim of our study was to describe oral health care behaviors among diabetic patients in Tunisia.
Method
This was a cross-sectional study involving diabetic patients hospitalised in the C department of the national institute of nutrition of Tunis between August and October 2016. A questionnaire contained a combination of open and close ended questions was specifically developed for this study. Patients were asked to answer questions related to their socio-demographic characteristics and their oral health behaviors (tooth brushing, mouth rinse and frequency of dental visits). Data about medical history, comorbidities and biology results were collected from medical file of patients.
Results
The mean age for the 101 diabetes recruited was 54.8 ± 14.9 years old, females comprised 57% of the population and the majority were having type 2 diabetes (83%). The mean number of years since diagnosis of diabetes was 12.8 ± 9.5 years. More than two thirds (70%) of participants were taking insulin. The average HbA1c was 10.4 ± 2.1%. The proportion of participants who had seen a dentist within the last year was 48%. Most of them (45%) visited their dentist mainly when urgent treatment was needed or because of pain. Only 12% visited a

dentist for check-up. Approximately 19% didn't visit a dentist at least 5 years ago and 8% did never consult a dentist. The higher the A1C was, the more recent was the dentist visit ($P=0.020$). Regarding tooth brushing, 34% admitted to brushing their teeth once a day or less, 45% brushed their teeth at least two times daily and 21% skipped tooth brushing altogether. We observed that women were more likely than men to brush twice daily ($P<0.0001$). Miswak use was reported by 33.7% of subjects. A minority (8%) reported using a mouth rinse. Tooth brushing frequency was negatively associated with tooth loss ($r^2=0.342$; $P=0.001$).
Conclusion:
Despite the greater risk for the development of periodontal disease, the oral self-care was poor among Tunisian diabetes. Promotion of oral self-care and regular dental check-ups are needed.

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Clinical evaluation of erectile dysfunction in diabetic patients by IIEF5 Score

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Introduction
The management of diabetes goes through the education but also the management of acute and chronic complications. Among the complications, erectile dysfunction are too often forgotten as they actually affect the quality of life. The repercussions of this complication incite the clinician to look for it among the other complications of diabetes. The aim of our study is to evaluate the prevalence of erectile dysfunction in a diabetic population and to evaluate its clinical severity.
Patients and methods
This is a prospective study of diabetic patients hospitalized for diabetes from January 2017 to April 2017. The types of diabetes included were type 1 and type 2 diabetes. Diagnosis of dysfunction Erectile was done at the time of hospitalization and the degree of severity was assessed by Urological Score IIEF5 Simplified International Index of Erectile Function interpreted as: Severe erectile dysfunction (score of 5–10), moderate (11–15), mild (16–20), normal erectile function (21–25) and uninterpretable (1–4).
Results
There were 114 patients with a mean age of 53.77 ± 10.8 years. The family history was type 2 diabetes in 78.9%, hyperrtension in 43.9%, and ischemic stroke in 16.1% of cases. Of the patients, 30.1% were hypertensive, 32.5% were dyslipidemic all under statins, 71.9% were smokers. Type 2 was predominant in patients in 91.2%. Treatment of diabetes was insulin-only in 48.1% of cases, oral antidiabetic alone in 18.4% and 32.5% in combination. Degenerative complications were present in 51.4%, with diabetic retinopathy in 51.4% of cases, diabetic neuropathy in 44.2% of cases and diabetic nephropathy in 18.2% of cases. The mean BMI of patients was $=26\pm5.6$ kg/m^2 with overweight in 28.4% of cases and obesity in 19.7% of cases. Erectile dysfunction affected 91.2% of the study population. The mean IIEF5 score was 11 ± 3, with 22.8% mild degree dysfunction, 55.7% moderate, and 20.3% dysfunction considered severe. The hormonal profile showed mean testosterone levels $=4.02\pm1.53$ ng/ml with a decreased levels in 61.1% of cases.
Conclusions
In addition to the high prevalence of erectile dysfunction in diabetics, this study also shows that it is important to rate the degree of severity of the dysfunction to better match the treatment. This is why erectile difficulties must be systematically detected at least annually, in the same way as another complication.

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Variability of glycemia and cognitive function in patients with type 1 diabetes mellitus

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Objective
To determine the effect of glycemic variability on cognitive function in patients with type 1 diabetes mellitus.
Materials
Thirty patients with type 1 diabetes mellitus were examined at the age of 29.7 (27.45–30.4) years, the duration of the disease was 19 (15.1–20.3) years. Patients were divided into 2 groups: 1st group ($n=15$) – patients with cognitive impairment, 2nd group ($n=15$) – without.
Methods
All patients were evaluated for cognitive status using the Montreal Cognitive Scale. The content of HbA1c was determined on DS5 Glycomat (Drew Scientific, The Netherlands). For the diagnosis of fluctuations in glycemia, continuous monitoring of glycemia was conducted using the iPro-2 (Medtronic, USA) and CareLink iProTM software. EasyGV calculator (2011) was used to analyze the variability of glycemia. The following indices were studied: mean glycemic mean (MEAN), standard deviation (S.D.), mean amplitude of glycemic fluctuations (MAGE), long-term glycemic index (CONGA), glycemia lability index (LI), hypoglycemia risk index (LBGI), hyperglycemia risk index (HBGI), mean hourly rate of change in glycemia (MAG). Statistical processing of the obtained data was carried out using the application software package R-system
Results
As a result of the study, patients with type 1 diabetes of the main group were diagnosed with cognitive impairment, the mean score was 23.8 ± 0.66, when in the control group it was 26.4 ± 0.13 ($t=3.6$, $P=0.001$). In the study of HbA1c in blood plasma, it was determined that the mean level in the main group was $10.5\pm1.3\%$, and in the control group it was 6.7 ± 0.23. % ($t=-2.5$, $P=0.015$). Significant difference in MEAN, S.D., CONGA, LBGI, HBGI, MAGE and MAG values between the groups is recorded. When performing the correlation analysis, it was shown that the level of HbA1c ($\chi2=-0.450$, $P=0.014$), as well as the parameters of the variability of glycemia-MEAN ($\chi2=-0.584$, $P=0.001$), S.D. ($\chi2$), affects the cognitive functions in type 1 diabetes. $=0.022$, $P=0.022$), CONGA ($\chi2=-0.853$, $P=0.001$), LBGI ($\chi2=-0.451$, $P=0.014$), HBGI ($\chi2=-0.053$, $P=0.003$), MAGE ($\chi2=-0.480$, $P=0.008$), MAG ($\chi2=-0.573$, $P=0.001$).
Conclusion
In patients with type 1 diabetes mellitus, hyperglycemia and hypoglycaemia, the duration of the increase in glycemia and the average fluctuation in glycemia may lead to a decrease in cognitive functions.

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Septicemia in diabetics in Tunisia: Study of 43 cases

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Diabetes is a factor favoring infections. Among which, the sepsis that becomes formidable and serious on this ground. The purpose of our work is to study the clinical, therapeutic and evolutionary features of sepsis in diabetics. A retrospective study of 43 cases of septicemia in diabetic patients collected at the service of Sfax Infectious Diseases. There were 22 men and 21 women, mean age 59 (20–78) years. Community origin was present in 88.4% of cases and nosocomial in 11.6% of cases. urinary symptomatology in 13 cases (30%), digestive in 8 cases (18.6%) and cutaneous in 12 cases (27.9%) The table was severe from the outset (sepsis or shock) in 13 cases. were gram-negative bacilli in 52% (including Escherichia coli in 31.8% of cases) and Gram-positive cocci in 49% (including Staphylococcus aureus in 62% of cases). The portal of entry was certain in 34 case (79%) and probable in 9 cases (21%): urinary (46.5%), cutaneous (39.5%) and endovascular (14%) One or more secondary locations were found in 14 patients (33%): osteo-articular (4 cases), renal (3 cases), pulmonary (3 cases), cutaneous (2 cases), cardiac (1 case) and abdominal (1 case). Treatment was adapted to the isolated germ in 76.7% d The average duration of effective treatment was 22 (10–60) days. The septicemia of the diabetic individualized by their greater frequency compared to the non-diabetic population. The germs in question are gram-negative bacilli as well as gram-positive cocci.

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An association of non-alcoholic fatty liver disease and autonomic neuropathy parameters in patients with type 2 diabetes

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Background
Non-alcoholic fatty liver disease (NAFLD) is metabolic disorder of the liver that is associated with type 2 diabetes.The relationship between NAFLD and diabetic neuropathy was still poorly understood. This study aimed to investigate whether the NAFLD is associated with the autonomic neuropathy parameters in patients with type 2 diabetes.
Methods
A total of 174 patients with type 2 diabetes were included in this study. Patients were divided into two groups based on the presence of NAFLD: 87 type 2 diabetes with NAFLD and 87 type 2 diabetes without NAFLD. The presence of NAFLD was determined in patients using abdominal ultrasonography. Anthropometric measurements, glycated hemoglobin, lipid profile, liver function test were assessed. Autonomic neuropathy testing was performed according to the ADA guidelines. They consists of the valsalva ratio, lying standing heart rate, R-R interval variation, postural hypotension, and sustained handgrip.
Results
Comparing to NAFLD group, mean age of non-NAFLD group was significantly higher (62.84 ± 11.93 vs 54.16 ± 12.93, $P < 0.05$). BMI, ALT and LDL levels were higher in NAFLD group than non-NAFLD group ($P < 0.05$). There was no difference of HbA1c level between two groups. In each autonomic function test parameter, there was no significant difference according to presence of NAFLD in type 2 diabetes patients, except BP response to sustained handgrip. Changes of autonomic function test parameters according to severity of fatty liver were only significantly different in heart rate response to Valsalva. Patients with severe fatty liver were higher in Valsalva ratio than mild and moderate severity groups ($P < 0.05$).
Conclusion
Our study showed that autonomic neuropathy parameters of type 2 diabetes did not demonstrate significantly consistent result according to presence of NAFLD. Further prospective studies are needed to elucidate the association of NAFLD and diabetic autonomic neuropathy.

Keywords: Non-alcoholic fatty liver disease, Diabetic autonomic neuropathy, Type 2 diabetes

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Characteristics of cardiovascular autonomic neuropathy depending on the type of diabetes and importanace of cardiovascular tests in diagnostics

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Purpose
The goal of the study was to determine: existence and degree of diabetic cardiovascular autonomic neuropathy (DCAN) depending on the type of diabetes; influence on systolic and diastolic function of myocardium and correlation with coronary disease and cardiovascular risk factors; possibility of early detection and diagnostic value of cardiovascular tests (CVT).
Methods
The study involved 90 participants: 30 patients with type 1 diabetes (T1DM), 30 patients with type 2 diabetes (T2DM) and 30 participants in the control group. Electrocardiogram, cardiac stress test and echocardiography has been done to all participants. Function of the autonomic nervous system was evaluated using 5 CVT: Valsalve maneuver, deep breathing, stand-up after lying position, orthostatic hypotension and Hand grip tests.
Results
The results showed that DCAN occurred significantly more often in patients with T2DM ($P < 0.001$). In patients with T1DM and T2DM with DCAN cardiac stress test was positive significantly more often ($P < 0.05$), i.e. correlation with coronary disease. Concerning coronary disease risk factors most common correlation was found with obesity and hypertension. Diastolic function of the left ventricle was significantly often impaired in patients with DCAN ($P < 0.001$), especially in T2DM. The most common pathological CVT in T1DM (71,4%), T2DM (83,3%) $P < 0.001$, was standup from lying position test.
Conclusion
Significant correlation between impaired diastolic function of the left ventricle and abnormal cardiac stress test results with DCAN indicates its significance in etiopathogenesis of diabetic cardiomyopathy and coronary disease. CVTs enable early detection of DCAN and objective cardiovascular evaluation.

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Importance of HBA1C level and BMI in patients with chronic kidney disease

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Purpose
Diabetic nephropathy is one of the leading causes of chronic kidney disease (CKD). Poor regulated glycemic control can result in progression of CKD. As diabetes mellitus (DM) and obesity can participate in development of atherosclerosis, the aim of this study was to assess the association of HbA1c and BMI in patients with CKD with intima-media thickness (IMT) as the early marker of atherosclerosis.
Methods
This cross-sectional study included 88 patients of all stages of CKD. Patients' average age was 62.84 ± 11.37 years. There were 56% female patients. 40% of patients had DM and 91% hypertension (HTA). HbA1c level, BMI, lipid and mineral status, kidney function and IMT were analyzed.
Results
DM cause CKD in 35.63% patients and HTA in 15%. Mean HbA1c level was 7.80 ± 1.28 and BMI 27.19 ± 3.59 kg/m^2. Average value of IMT was 1.09 ± 0.25 mm and mean estimated glomerular filtration rate 40.59 ± 31.15 μmol/l. HbA1c level positively correlated with serum calcium and phosphate product (CaxP) level ($r = 0.4$, $P < 0.05$), whereas BMI with IMT level ($r = 0.28$, $P < 0.01$). Binary logistic regression showed patients' age as the independent predictor of pathological IMT value. HTA and CaxP level were the best predictors of the occurrence of carotid plaque.
Conclusions
Our study showed that HbA1c level is associated with the CaxP in patients with CKD. BMI was associated with early signs of atherosclerosis. Glycemic control and nutritional status in patients with CKD should be carefully monitored and tailored to each individual patient.

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P415

The results of questionnaire by comprehensive symptom profile diabetes mellitus hypoglycemia nodule in type 2 diabetes patients

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The aim
To evaluate the results of Questionnaire by Comprehensive Symptom Profile Diabetes Mellitus hypoglycemia (CSP-DM-HypoGl) nodule in type 2 diabetes patients
Material and methods
Under our supervision in the departments of the Center of Endocrinology of PH Ministry of RUz in the period from September 2016 for December, to 2017, 20 patients were observed with DM 2, men – 9, women-11; 54.5 ± 1.5 m/$61,6 \pm 1.8$ w years old. The remoteness of disease hesitated in limits from 7 to 9 years. All patients were observed by standard rules.
Results
Patients were distributed on 2 groups: 1 gr – 10 patients (5/5), which received IIT, 2 gr – 10 patients (4/6) on CT (insulin + Metformin, SM, etc). We studied results of CSP-DM-HypoGl in all patients, which has 28 questions. On the data of interpretation of CSP-DM-HypoGl, if patients results achieve 1–4 in middle: this is lower degree of hypoglycemia, if 5-6 – middle degree of hypoglycemia and 7 >: higher degree of hypoglycemia. In 1 st group of patients we found of CSP-DM-HypoGl in range of 7 ± 0.3, which submit higher degree of episodes of hypoglycemia in this group. Patients had such symptoms as weakness, headache,

disorders of sleep. In the 2 nd group of patients we found middle range of CSP-DM-HypoGl 5,5 ± 0.4, which submit middle degree of episodes of hypoglycemia in this group.
Conclusions
The using of CSP-DM-HypoGl gives possibility to evaluate the degree of symptomatic hypoglycemia in patients with DM 2

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Comparitive angiographic profile in diabetic and non-diabetic patient (retrospective study)

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Background
Diabetes is one of the risk factor for coronary disease. Patient with diabetes have a increased prevalence and incidence of coronary vessels disease compare with the people without diabetes in the general population.
Aim and objectives
To compare the study of angiographic coronary results in the patient with and without diabetes.
Materials and methods
172 pacients; 66 with diabetes and 106 without diabetes was admitted to our hospital. In a retrospective study we evaluated the results of coronary angiography examination. The examination was performed to the patients with acute coronary syndrome or in patients with positive cardiac stress test.
Results
38% (66) of the patients was with diabetes or prediabetes compare with 62% (106), without diabetes. In diabetes patients: 74% (49) males and 26% (17) females. Average ages in diabetes patients was 63.1 ± 9 years old and average HbA1c values was 7.8 ± 1.5%. Angiography results in patients with diabetes: 42.5% (28) with triple multi vessel; 24.5% (16) two vessel; 21% (14) one vessel and 12% (8) without significant stenosis. Angiography results in patient without diabetes: 23% (24) triple multi vessel; 18% (20) two vessel; 26% (28) one vessel and 25% (26) without significant stenosis.
Conclusions
The incidence of multi vessel coronary artery disease was higher in diabetes patients compare to non diabetes patient. The majority cases in patients with diabetes have two or three vessel coronary artery disease.

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Thiol-disulfide homeostasis, total antioxidant capacity and advanced oxidant protein products in patients with diabetic peripheral neuropathy

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Aim
In our study, we aimed to evaluate the relationship between oxidative stress markers such as total antioxidant capacity (TAC), advanced oxidant protein products (AOPP) and thiol-disulfide homeostasis parameters and diabetic peripheral neuropathy (PNP), an important microvascular complication of diabetes mellitus (DM).
Material and methods
80 (male/female = 34/46) patients with type 2 DM and 19 healthy controls were included in the study. All patients were assessed for PNP by Michigan Neuropathy Screening Test (MNTT) and Electroneuromyography (EMG). TAC, AOPP and total thiols, native thiols and disulfide levels of thiol-disulfide homeostasis parameters were studied in serum samples of patients and controls.
Results
There was no statistically significant difference between serum TAC, AOPP levels and thiol-disulfide homeostasis parameters when patients were grouped as those with and without PNP according to EMG or MNTT results. Regrouping was made and the patients were classified as having PNP if both EMG and MNTT results were positive. If both EMG and MNTT results were negative, they were classified as patients without PNP. Patients with discordant results were excluded. According to the regrouping, serum HbA1c (9.5 ± 2.0% vs 8.0 ± 1.8%; $P = 0.019$) and triglyceride levels (204.4 ± 77.0 vs 151.7 ± 58.5 mg/dl, $P = 0.014$) were significantly higher while serum total thiol levels (540.4 ± 9.9 vs 566.7 ± 2.6 μmol/l, $P = 0.038$) were lower in diabetic patients with PNP compared to diabetic patients without PNP. There was no difference between serum TAC, AOPP, native thiol and disulfide levels in patients with and without PNP. However, when compared with the control group, serum CRP, AOPP, total thiol and native thiol levels were found higher in patients with type 2 DM ($P = 0.001$, $P = 0.002$, $P = 0.02$ and $P = 0.03$; respectively).
Conclusions
In our study, there was no significant increase in serum TAC, AOPP, and thiol-disulfide homeostasis parameters, which are indicative of oxidative stress, in diabetic patients with PNP compared to those without PNP. These results suggest that the oxidative stress parameters assessed in our study are more closely related to the presence of diabetes rather than the presence of PNP.

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Association of dislipidemia and glycemic control in patients with type 1 diabetes mellitus

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Objective
Assessment of the association of dyslipidemia and glycemic control in patients with type 1 diabetes mellitus
Materials and methods
200 patients with DM 1 were examined (mean age 29.14 ± 7.33 years, duration of DM 1 10.00 ± 7.33 years). The study of daily glucose dynamics was carried out by the continuous glucose monitoring system (CGMS) of Medtronic MINIMED, USA. HbA1c and lipid metabolism parameters were determined by the biochemical analyzer ARCHITECT c8000, Abbott.
Results
The correlation analysis revealed a direct relationship between the level of HbA1C and the level of total cholesterol ($rs = 0.21$; $P < 0.05$), triglycerides ($rs = 0.23$; $P < 0.05$), VLDL ($rs = 0.23$; $P < 0,05$) and between the duration of hyperglycemia and the level of TG ($rs = 0.16$; $P < 0.05$), VLDL ($rs = 0.19$; $P < 0.05$), total cholesterol ($rs = 0.15$; $P < 0.05$). The duration of hypoglycemia is negatively associated with the atherogenic index ($rs = -0.32$; $P < 0.05$). The minimum level of glucose directly depends on the level of TG ($rs = 0.14$; $P < 0.05$), VLDL ($rs = 0.17$; $P < 0.05$), total cholesterol ($rs = 0.17$; $P < 0.05$), the atherogenic index ($rs = 0.23$; $P < 0.05$) (Table 1).
Conclusion
The association of atherogenic lipid profile with an increase in the level of HbA1c and the presence of hypoglycemic states has been proved.

Table 1 Laboratory characteristics of glycemic control and lipid metabolism.

Indicator	Me (25;75)
HbA1c, %	9,00 (7,70; 10,60)
The minimum level of glucose, mmol/l	2,70 (2,20; 4,10)
The average level of glucose, mmol/l	10,10 (8,30; 12,20)
Duration of hypoglycemia, %	5,00 (2,00; 10,00)
Duration of hyperglycemia, %	50,00 (32,00; 68,00)
Total cholesterol, mmol/l	4,60 (4,00; 5,20)
Triglycerides, mmol/l	0,92 (0,68; 1,37)
HDL (high-density lipoproteins), mmol/l	2,08 (1,55; 2,89)
LDL (low-density lipoproteins), mmol/l	1,73 (1,34; 2,42)
VLDL (very low density lipoproteins), mmol/l	0,40 (0,30; 0,62)
Atherogenic index	2,10 (1,60; 2,70)

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Urinary neutrophil gelatinase-associated lipocalin (NGAL) as a marker of diabetic nephropathy in type 1 diabetic patients

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Aims
Glomerular and tubulointerstitial damage plays a role in renal function failure in diabetic patients. While both serum and urine levels of neutrophil gelatinase-associated lipocalin (NGAL) show significantly increased levels in acute renal pathologies, the NGAL increase in active phase indicates a reversible condition in chronic cases. In this study, we determined if urinary excretion of NGAL can be used as an early indicator of diabetic nephropathy, which causes chronic renal damage. We compared urinary NGAL excretions both between type 1 diabetic patients and the healthy control group and between the patients with and without albuminuria within the type 1 diabetic group. The goal of this study was to investigate if NGAL excretion is sensitive enough for clinical use as an early indicator of nephropathy in diabetic patients.
Methods
Fifty-two type 1 diabetic patients and 30 healthy volunteers participated in the study. The diabetic participants were separated into two groups as follows: a normoalbuminuria group consisting of those with an albumin/creatinine ratio less than 30 mg/g and an albuminuria group consisting of those with an albumin/creatinine ratio equal or greater than 30 mg/g. Albumin, creatinine and NGAL were measured in the morning spot urine samples of both the patient and the control group.
Results
The median NGAL level of diabetes patients was 21.1 ng/ml, which was significantly higher than the corresponding value of 11.9 ng/ml in controls. When diabetic patients were compared as those with and without albuminuria, the median urinary NGAL levels of normoalbuminuria and albuminuria were 24.7 and 16.1 ng/ml, respectively, but the difference was not statistically significant.
Conclusion
In type 1 diabetic patients, urinary NGAL excretion was increased but was not significantly correlated with urinary albumin excretion. The greater amount of NGAL excretion among diabetic patients may be due to diabetic nephropathy with possible tubulointerstitial damage pathologies. In this regard, urinary NGAL excretion should not be used as an alternative to microalbuminuria in detecting diabetic nephropathy. There is a need for further studies examining the long-term changes in NGAL excretion levels and renal functions.

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APOB/APOA1 ratio is associated with metabolic syndrome in type 2 diabetes mellitus women with ischemic cardiomiopathy

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Background
Retrospective, transversal and analytical study was designed to determine the relationship between ApoB/ApoA1 ratio, Non-HDL-Cholesterol/HDL-Cholesterol ratio and Metabolic Syndrome (MetS) in type 2 diabetes mellitus (T2DM) patients attending routine follow-up in outpatient clinic from Madrid.
Methods
The study was performed at the University Hospital Infanta Leonor, a public health center, and specialized secondary referal, which provides services to the 31 urban district of Madrid, Spain (Vallecas district, 300 000 people). 100 T2DM and high cardiovascular risk subjects, who attended the clinic between January of 2014 and June of 2017 for a routine follow-up were enrolled in this study. A blood sample was taken every 6 months in all patients and an average of 4-5 values prior to analysis were performed. Diagnosis of MetS was made according to definition of modified NCEP-ATPIII (National Cholesterol Education Program's Adult Treatment Panel III) 2. The following variables were measured in serum or plasma samples: Colesterol, HDL-Cholesterol, ApoB, ApoA1, triglycerides, high-sensitivity C Reactive Protein, ferritin, and transferrin. LDL-Cholesterol was calculated (Friedewald). Median comparisons were done with the Mann Whitney U test. Relationships between variables were measured with Spearman correlation test. Multivariate regression analysis was performed with ApoB/ApoA1 and Non-HDL-Cholesterol/HDL-Cholesterol ratios as dependent variables and age, gender and other cardiovascular risk factors as independent variables, after an outlier identification. A level of $P<0.05$ was considered statistically significant (SPSS, v. 21.0).
Results
We found associations, that remain after adjusting comorbidities and risk factors, between MetS and ApoA1 ($R^2=0.164$, $P=0.028$), ApoB/ApoA1 ratio ($R^2=0.187$, $P=0.001$); and Non-HDL-Cholesterol/HDL-Cholesterol ratio ($R^2=0.269$, $P=0.0001$). Moreover, there is an association between women with MetS and ApoB/ApoA1 ratio and ischemic cardiomyopathy that remain also after adjusting comorbidities and risk factors ($R^2=0.160$, $P=0.032$).
Conclusions
We found that both lipidic ratios are adequate for predicting MetS in T2DM patients of the population studied. ApoB/ApoA1 ratio shows to be a better cardiovascular risk marker, in women with MetS than in men. New studies should be carried out to confirm this finding.

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P421

Soluble dipeptidyl peptidase-4 activity is associated with decreased renal function in patients with type 2 diabetes

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Objective
Dipeptidyl peptidase (DPP)-4 is highly abundant in the kidney. In various chronic inflammatory diseases, soluble DPP-4 activity is used as a marker for diabetes, coronary artery disease and cancer. This study examined the association between serum soluble DPP-4 levels and renal function or cardiovascular risk in patients with type 2 diabetes mellitus.
Research design and methods
Soluble DPP-4 activities were measured retrospectively in a total of 120 patients with type 2 diabetes in the preserved samples from our previous coronary artery calcium score study.
Results
The mean soluble DPP-4 level was 645 ± 152 ng/ml. Univariate analyses revealed that soluble DPP-4 activities were significantly correlated with total cholesterol ($r=0.214$; $P=0.019$), serum creatinine ($r=-0.315$; $P<0.001$), and estimated glomerular filtration rate by the modification of diet in renal disease (MDRD) ($r=0.303$; $P=0.001$). Associations between soluble DPP-4 with serum creatinine and GFR by the MDRD equation remained significant after adjustment for body mass index, age, and duration of diabetes. However, there was no association between soluble DPP-4 levels and body mass index, waist circumference, or coronary artery calcium score (CACs).
Conclusions
These data suggest that soluble serum DPP-4 activity might be used as a potential biomarker of deteriorated renal function in patients with T2D.

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Predictors of the development of androgen deficiency in men with type 1 diabetes mellitus

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The aim of the study is the search of predictors of the development of androgen deficiency in men with 1 diabetes mellitus type 1. The study included 211 men

with type 1 diabetes mellitus aged 18–55 years. The median age of men was 39.00 (30.00; 45,00) years, the median duration of diabetes mellitus type 1 was 12,00 (7,00; 22,00) years. As a result of the research, it was found that an increase in the patient's age significantly increased the risk of developing androgen deficiency (b = 0.07, Exp (b) = 1.08 (1.00 ÷ 1.16), $P < 0.05$). The age of smoking experience also had a significant effect on the risk of developing androgen deficiency (b = 0.06; Exp (b) = 1.07 (1.10–1.13), $P < 0$, 04). The relative risk of developing (RR) androgen deficiency in men with a smoking experience of more than 7 years was 3.76 and was statistically significant (95% CI = 1.07 ÷ 13.25). With an increase in the level of glycated hemoglobin, the risk of developing androgen deficiency also increased significantly (b = 0.08; Exp (b) = 1.01 (1.00 ÷ 1.02), $P < 0.04$). The exceeding of the glycated hemoglobin level above 7.5% demonstrated a statistically significant RR = 6.71 (95% CI = 1.19 ÷ 37.86). The reduction of LDL decreased the risk of developing androgen deficiency in the men surveyed at the level of a stable trend (b = −0.45; Exp (b) = 0.64 (0.35 ÷ 1.18), $P < 0.10$). At an LDL level of less than 3.50 mmol / l, the RR of androgen deficiency was 0.29 and was statistically significant (95% CI = 0.09–0.97). The rise in VLDL significantly increased the risk of androgen deficiency (b = 0.71; Exp (b) = 2.04 (1.11 ÷ 3.76), $P < 0.02$). At a VLDL level of 0.42 mmol/L, the RR was 2.58 (95% CI = 1.38–3.29). As can be seen from the data provided, unsatisfactory compensation of type 1 diabetes mellitus increases the risk of developing androgen deficiency in men.

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P423

Relationship between serum levels of HDL cholesterol subclasses and carotid intima media thickness in patients with type 1 diabetes mellitus

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Aim
We aimed to investigate the possible relationship between HDL cholesterol subclasses and carotid intima media thickness (CIMT) in patients with type 1 diabetes mellitus (DM).
Material and methods
Sixty-two (female/male: 33/29, mean age: 33.3 ± 8.5 years) patients with type 1 DM at least 5 years and 20 (female/male: 10/10, mean age: 30.4 ± 5.6 years) healthy controls were included in the study. After physical examination and anthropometric measurements of all volunteers were performed, HDL2 and HDL3 cholesterol levels were studied from the serum samples which were taken following an 8–10 hour fasting period. CIMT measurements were performed to evaluate the existence of subclinical atherosclerosis by an experienced radiologist.
Results
There was no statistically significant difference between the two groups in terms of age, gender distribution, blood pressure control, anthropometric data, serum total cholesterol, LDL cholesterol, triglyceride, HDL cholesterol, ALT and creatinine levels. The mean HbA1c level was 8.1 ± 1.1% in patients with type 1 DM. The mean serum HDL2 cholesterol level was 17.3 ± 10.7 mg/dl in the patient group and 18.3 ± 7.2 mg/dl in the control group. The mean serum HDL3 cholesterol level was 27.5 ± 11.8 mg/dl in the patient group and 28.8 ± 8.6 mg/dl in the control group. No statistically significant difference was found between the groups in terms of serum HDL2 and HDL3 cholesterol levels ($P = 0.22$ and $P = 0.4$, respectively). The CIMT measurements were not different between the patient and the control groups (0.5 ± 0.2 mm vs 0.4 ± 0.1 mm; respectively) ($P = 0.23$). When both groups were evaluated together, there was no statistically significant correlation between serum HDL2 cholesterol levels and CIMT, but there was a negative correlation between serum HDL2 cholesterol levels and body mass index and waist circumferences ($r = -0.352$; $P = 0.001$ and $r = -0.236$; $P = 0.033$, respectively). There was no correlation between serum HDL3 cholesterol levels and any other study parameter including the measurement of CIMT. While serum HDL3 cholesterol levels in female patients with type 1 DM were higher than the male patients, serum HDL2 cholesterol levels were higher in females compared with the males in the control group ($P = 0.019$ and $P = 0.026$).
Conclusions
In our study, there was no relationship between serum HDL2 and HDL3 cholesterol levels and CIMT measurements in patients with type 1 DM. There is a need for additional prospective studies to demonstrate possible antiatherosclerotic effects of HDL cholesterol subclasses.

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P424

Dyslipidemia: type 1 diabetes vs. type 2 diabetes

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Lipid abnormalities are common in diabetic patients, increasing their cardiovascular risk. The aim of our study is to compare the lipid profile between type 1 and type 2 diabetics. This is a retrospective study of 100 patients, half of them have type 1 diabetes (group 1) and the other half have type 2 diabetes (group 2), hospitalized in department A of the National Institute of Nutrition of Tunis between January 2017 and June 2017. Type 2 diabetics were older than type 1 diabetics. The sex ratio was 0.67 in the first group and 1.17 in the second group. Diabetes evolved from an average of 8.55 years in the 1st group and 11.78 years in the 2nd. It was poorly balanced in both groups with the averages of HbA1c and fasting glucose respectively at 10.72% and 12.54 mmol/l in the 1st group and 10.46% and 10.81 mmol/l in the 2nd group. It was noticed that, for the 2nd group, the triglycerides levels were statistically higher (1.92 mmol/l vs 1 mmol/l; P value < 0.001) and the HDL cholesterol levels were lower (1.09 mmol/l vs 1.27 mmol/l; P value = 0.009). We did not find a statistically significant difference in LDL cholesterol levels between the two groups (1.01 g/l in the 1st group and 1.20 g/l in the second group). Our results are in line with the literature. In fact, our type 2 diabetics had a higher triglyceride level and a lower HDL-c level compared with type 1 diabetics. However, the LDL-c level, the most atherogenic fraction of cholesterol, does not seem to be influenced by the type of diabetes.

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P425

The comparison of serum cerebellin and catecholamine levelsin patients with newly diagnosed hypertension and type 2 diabetic whose had newly diagnosed hypertension

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Background/purpose
The combination of DM and HT accelerates vascular complications and increases the risk of mortality and morbidity. Hypertension is seen in half of diabetic patients. HT can be detected in approximately 40% of newly diagnosed diabetic patients. DM frequency increased 2.5 times in hypertensive patients. The association of HT and DM is due to the common mechanism responsible for the pathogenesis of both diseases. There is a limited number of studies investigating the association of HT and DM with catecholamines and the molecule called cerebellin, which is involved in the synthesis of catecholamines, has not yet been studied. Therefore, in this study, we aimed to determine how catecholamine and cerebelline levels were affected both before and after treatment in urine and blood of patients with HT and HT + DM.
Method
This study included 30 patients with newly diagnosed hypertension, 30 patients with previously diagnosed diabetes mellitus and new hypertension, and 30 healthy volunteer were included to the study. Both before and after treatment,

urine and blood samples were taken. Cerebelline, adrenaline, noradrenalin, metanephrine and normetanephrine levels were measured by ELISA. Other biochemical parameters (FBG, HbA1c, LDL, TG) were measured by autoanalyzer. In addition, the clinical characteristics of the collected patients were also recorded including age, gender, blood pressure and BMI.
Result
The BMI profile was similar among control, HT and HT + DM groups ($P > 0.05$). There was a significant decrease in blood and urine cerebellin, metanephrine and normethanephrine levels in the study patients compared with the control group, both before and after treatment ($P < 0.05$). When compared with the control group, the adrenaline levels in both urine and blood were increased in HT and HT + DM groups ($P < 0.05$). When compared with the control group, a significant increase in blood noradrenalin level was observed in HT group but decreased in HT + DM group. In addition to, when compared with control group, the urine noradrenaline level was increased in both HT and HT + DM groups ($P < 0.05$).
Conclusion
This result suggest that there is a relationship between cerebellin, catecholamine and catecholamine metabolites in HT and HT + DM patients. In the future, there is a need for further studies on the possibility that these biomarkers can give an idea about the etiopathogenesis of diseases such as HT, DM.
Key Words: Hypertension, diabetes mellitus, cerebellin, catecholamines
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P426

The prevalence of microvascular complications in the adults with type 1 diabetes and the glycemic control in the Republic of Belarus

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According to the current expert recommendations it is advisable to screen microvascular complications: diabetic peripheral polyneuropathy (DPN), diabetic retinopathy (DR), diabetic nephropathy (DN) in all patients with type 1 diabetes mellitus (T1D) and disease duration of 5 years. Therefore, the aim of the study was to assess the clinical and laboratory parameters of patients with type 1 diabetes at the age of 30−45 years with duration of the disease 5–15 years, taking into account adherence to the implementation of recommendations for the control of glycemia.
Materials and methods
360 T1D patients, 196 (54.4%) men and 164 (45.6%) women were examined. The average age of the patients was 37.9 ± 4.5 (37.4−38.4) years, the age of diabetes onset – 28.1 ± 6.2 (27.5−28.8) years, duration of the disease – 9.0 (7.0−12.0) years, body mass index – 24.8 ± 3.95 (23.6−25.2) kg/m^2. The study carried out a detailed clinical examination of patients with medical record analysis. The study was conducted within the framework of the nationwide action 'Early Detection of Chronic Complications of Type 1 Diabetes Mellitus in Adults'. Patients completed questionnaires of adherence to the implementation of recommendations for the glycemic control, the results of which were divided into two groups: 1st group (Gr1) − 257 (71.4%) people − predominantly compliant patients, 2nd (Gr2) − 103 (28.6%) people − mostly not committed to the control of glycemia. To verify the DPN the Vibratip device also used.
Results
In 36.9% cases DPN was diagnosed; DR – in 21.7%, DN − in 40.6%, albuminuria – in 38.1% cases. Microvascular diabetic complications were in 270 (75%) patients. The level of $Hb_{A1c,}$ used to estimate the compensation of glycemia, averaged 8.37 ± 1.83 (8.18−8.56), while in Gr1 the index was significantly lower than in Gr2: 8.20 ± 1, 83 vs 8.80 ± 1.75%, however, in both groups, the target values were not achieved. There were significant differences in groups in the presence of DPN − 33.5 vs 45.6% ($\chi^2 = 4.67$, $P = 0.030$), microvascular complication − 71.6 vs 83.5% ($\chi^2 = 5.55$, $P = 0.018$). However, there were no differences in the prevalence groups of DN − 62.6 vs 51.5% ($\chi^2 = 4.67$, $P = 0.051$), albuminuria 35.4 vs 44.7% ($\chi^2 = 4.67$, $P = 0.030$), DR − 51.4 vs 54.4% ($\chi^2 = 2.66$, $P = 0.102$).
Conclusions
In 75% cases of T1D fixed microvascular complications. Adherence to the control of glycemia without reaching the target values is associated with the diabetic neuropathy, but does not affect the development of diabetic retinopathy and nephropathy.
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P427

Inflammation in patients with diabetic nephropathy receiving different classes of glucose-lowering medications: serum levels of interferon gamma

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Proinflammmatory cytokines including interferon gamma (IFNg) are known to be involved in the pathogenesis of diabetic nephropathy. The aim of this study was to assess serum level of IFNg and its clinical correlates in patients with type 2 diabetes and early CKD receiving different types of treatment. We investigated 64 patients with type 2 diabetes and CKD stages 1-3. Group 1 included 20 patients on insulin therapy. Group 2 included 44 patients on metformin or combined oral hypoglycemic therapy. Groups were comparable on the basis of sex, age, body mass index and eGFR. In addition to routine clinical tests, we measured serum levels of ferritin, homocysteine, interleukin-6 and IFNg. Mann-Whitney *U*-test and Spearmen's correlation coefficient (rs) were used for statistical analysis. Serum level of IFNg was elevated in 20.0% patients from group 1 and 31.8% patients from group 2. Mean level of this cytokine was significantly higher in group 2 as compared to group 1 (14.6 ± 2.4 pg/ml vs. 6.5 ± 1.7 pg/ml, respectively, $P = 0.018$). In both groups serum concentration of IFNg had no significant correlations with age, body mass index, eGFR (CKD-EPI), albuminuria, hemoglobin, homocysteine, total cholesterol, lipid fractions, and interleukin-6. Only in group 1 (but not in group 2) the level of IFNg correlated with serum ferritin level (rs = −0.629, $P = 0.003$) and platelets count (rs = 0.547, $P = 0.013$). The results of the study suggest that insulin therapy is associated with lower serum level of IFNg in patients with type 2 diabetes and early CKD after adjustment for sex, age, body mass index and eGFR. This could be related to anti-inflammatory effects of insulin. In insulin-treated patients, serum level of IFNg correlates negatively with serum ferritin level and positively – with platelets count.
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P428

The relationship between morbidity and mortality and HbA1c level in major surgery applied with diabetic patients

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Background
Diabetes Mellitus (DM) is a disease that increasing in prevalence rapidly in our country and in the world with the increase of sedentary life and unhealthy nutrition. The risks of surgery applied in diabetic patients differ according to other patients.
Aim
We aimed to investigate the relationship between the preoperative HbA1c levels and the complications and mortality rates in the postoperative period in patients with diabetes diagnosis and was applied major surgical treatment.
Method
We included patients who underwent major surgery between January 1, 2015 and December 31, 2016 in our hospital and who had been diagnosed with type 2 diabetes and had been looked at HbA1c levels preoperatively. A total of 1013 patients whose file data were completely accessed, were included in the study. Preoperative HbA1c levels of the patients and complications seen within the first 7 and first 30 days postoperatively were recorded.
Results
Forty nine (4.8%) of the patients were exitus in the hospital while 964 (95.2%) of patients were discharged. Preoperative HbA1c levels of the patients were found to be predictive marker of mortality in the first 7 and 30 days postoperatively ($P < 0.05$). Preoperative HbA1c value was found to be very significant in predicting the complication, wound infection, total infection risk within the first 7 and 30 days postoperatively ($P < 0.001$).
Discussion
It is very important to base HbA1c levels on preoperative surgical risk assessment in diabetic patients. Better provision of long-term glycemic control in patients

planned elective surgery and have high HbA1c levels may significantly reduce postoperative mortality and complications.

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P429

The relationship between intertemporal choice and blood glucose control in type 2 diabetes

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The objectives of this study were to investigate intertemporal choice in patients with type 2 Diabetes and whether blood glucose control is related to intertemporal choice. Ninety seven diabetes patients (41 inpatients and 56 outpatients) were recruited. All patients were subjected to the following tests: DM Distress Scale (DDS), Beck Anxiety Inventory (BAI), the Center for Epidemiologic Studies Depression Scale (CES-D) and the Big Five Inventory-K-10 (BFI-K-10). 73 of recruited patients performed the delay discounting task (DDT). Compared to the outpatient group, the inpatient group showed higher delayed reward discounting rate in DDT. Outpatient group showed higher score in the agreeableness than inpatient group. And Inpatient group scored higher than outpatient group in the score of the Beck-anxiety inventory. The anxiety score and DDT were negatively correlated, and anxiety score and HbA1c were positively correlated. In addition, anxiety scores were positively correlated with neuroticism, diabetes distress scores, depression scores and negatively correlated with agreeableness scores. Agreeableness showed a negative correlation with HbA1c and 180days′ indifferent points, respectively. Agreeableness was also significantly associated with diabetic stress, anxiety, depression and there was a positive correlation with conscientiousness. In this study, we found that there is a difference in intertemporal choice between inpatient and outpatient groups. In addition, it was confirmed that the difference of personality traits and negative emotions between the two groups was related to the selection of intertemporal choice and related to the control of blood glucose.

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P430

Characteristics of diabetic foot patients admitted to department of endocrinology and metabolic diseases at ankara university, faculty of medicine

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Introduction
Diabetic foot is one of the important and destructive complications of diabetes. During the life time of a diabetic patient, the risk of developing foot ulcers is around 5–15%, and about 20–25% of the causes of hospitalization in diabetic patients are due to foot ulcers. 40–80% of foot ulcers can be infected and resulted in osteomyelitis. Hospitalization due to osteomyelitis is 12 times more in diabetic patients than in non-diabetic population.
Objective
It is aimed to evaluate retrospectively, the patients admitted due to diabetic foot to the Department of Endocrinology and Metabolic Diseases at Ankara University, Faculty of Medicine in the last 1 year.
Method
Information from the data processing system and file records about patient age, gender; smoking habbits, diabetes education, diet compliance; duration of diabetes; presence of other micro/macrovascular diabetic complications, diabetic foot development and progression, and HbA1c levels were obtained. Fifty four diabetic foot patients were evaluate eighteen of whom were outpatient, and thirty six of whom were inpatient.
Results
The majority of patients were suffering from type 2 diabetes melltus (96%). All chronic micro/macrovascular complications especially peripheral arterial disease were detected at high rates in diabetic foot patients. Trauma and burns (respectively, 34% and 10.6% of patients) were detected as major triggering factors. The mean duration of diabetic foot development was determined as 150 days at inpatients and 60 days at outpatients. Most of outpatients (55.6%) were presented with Wagner 1 diabetic foot ulcers and 50% of the inpatients were presented with Wagner 3-4-5 diabetic foot ulcers.
Conclusions
Diabetic foot evaluation, treatment and follow-up requires a multidisciplinary approach. In terms of diabetic foot development, it is very important to identify high-risk patients and determine the appropriate treatment plan.
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Table 1 Characteristics of patients

	Outpatient (*n*:18)	Inpatient (*n*:36)
Gender male/female (%)	13 (72.2%)/5 (27.8%)	21 (58.3%)/15 (41.7%)
Age (years)	65.3 (52–78)	62.9 (40–80)
Duration of diabetes (years)	21.2 (3–40)	19.9 (4–40)
Type 2 DM (%)	18 (100%)	33 (91.7%)
Hba1c (%)	10.4 (6.9–14.4)	9.3 (6.1–14.2)
Diabetes education (%)	2 (11.1%)	15 (41.2%)
Diet compliance (%)	2 (11.1%)	8 (19.4%)
Smoking (%)	4 (22.2%)	19 (52.8%)

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P431

Atherosclerosis in women of reproductive age with type 2 diabetes mellitus and polycystic ovary syndrome

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Introduction
The aim of this study was to investigate the degree of atherosclerosis in women of reproductive age with type 2 diabetes mellitus (T2DM), with and without polycystic ovary syndrome (PCOS).
Patients and Methods
71 women (mean age 43.2 y) with T2DM treated with diet or oral anti-diabetic medications and 36 controls were studied. According to menstrual cycle and clinical hyperandrogenism, patients with T2DM were classified into two subgroups, 53 without PCOS (T2DM+PCOS-) and 18 with PCOS (T2DM+PCOS+). After overnight fast in the first phase of menstrual cycle, hormonal and biochemical measurements were recorded, while the carotid intima-media thickness (IMT) was measured.
Results
Women with T2DM presented significantly higher BMI (34.5 ± 6.39 vs 27.9 ± 6.1, $P<0.001$), waist circumference (105.3 ± 14 vs 86.9 ± 11.2, $P<0.001$), hirsutism (1.78 ± 0.9 vs 1.15 ± 0.3, $P<0.01$) and family history of T2DM (82.5% vs. 34.6%, $P<0.002$). They also had significantly higher total testosterone (0.62 ± 0.21 vs 0.45 ± 0.11, $P<0.001$), insulin (17.8 ± 11.9 vs 9.8 ± 3.6, $P<0.002$), triglycerides (131 ± 23 vs 95 ± 67, $P=0.02$) and LDL cholesterol levels (132 ± 31 vs 114 ± 23, $P=0.025$), while lower SHBG (34.3 ± 16.2 vs 53.9 ± 18.7, $P<0.001$) and HDL cholesterol levels (47.1 ± 12.8 vs. 57 ± 10.9, $P<0.001$) compared to controls. T2DM+PCOS+ patients reported a significantly higher rate of gestational diabetes (37.5% vs. 8.3%, $P<0.05$), younger age of diagnosis of T2DM (32.8 ± 5.7 vs. 39.7 ± 6.1, $P<0.001$) and presented significantly higher waist circumference (115 ± 12.8 vs. 99 ± 11.1, $P<0.01$) compared to T2DM+PCOS- patients. They also had higher levels of total testosterone (0.75 0.22 vs 0.54 ± 0.16, $P=0.01$) and insulin levels (24 ± 15.8 vs 14.4 ± 7.5, $P<0.05$), lower SHBG (26.1 ± 9.5 vs 39.8 ± 17.6, $P<0.001$) and HDL-cholesterol levels (41.4 ± 11.2 vs 50.8 ± 12.6, $P<0.001$). The degree of atherosclerosis as assessed by IMT was significantly higher in patients with T2DM compared to controls (0.065 ± 0.007 vs 0.056 ± 0.008, $P<0.001$), but did not differ significantly between the two subgroups of patients with T2DM.
Conclusion
The results of this study provided evidence that women of reproductive age with T2DM present early atherosclerosis compared to healthy controls, but the

coexistence of PCOS does not seem to additionally deteriorate the degree of clinical atherosclerosis.

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P432

Association of adverse pregnancy outcomes with glycemic cut-offs stated by the IADPSG, POGS and WHO diagnostic criteria for gestational diabetes mellitus in De La Salle University Medical Center (DLSUMC), Cavite, Philippines from January 2012 to December 2015

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Objectives
To determine the association between adverse pregnancy outcomes with each of the 75 g OGTT cut-off values prescribed by the World Health Organization (WHO), Philippine Obstetrical and Gynecological Society (POGS), and the International Association of Diabetes in Pregnancy Study group (IASDPG) criteria to help define more appropriate glycemic cut-off levels for Filipinas.
Methodology
Retrospective Cohort study of pregnancy deliveries in De La Salle University Medical Center (DLSUMC), Cavite, Philippines from January 2012 to December 2015. Subjects were >18 years old with a singleton pregnancy, a 75-g OGTT result, and complete medical record without other existing comorbidities or illnesses that may affect outcomes. Maternal and neonatal outcomes were recorded and their association with the different glycemic cut-offs stated by the WHO, POGS and IADPSG were analyzed.
Results
Total of 195 subjects were included. Patients with an FBS >126 mg/dl were 5.7 folds more likely to have pre-eclampsia ($P=0.020$) and 3.2 folds likely to have preterm delivery ($P=0.44$), however, there is a significant number of GDM patients (22.3%) not diagnosed by this higher FBS cut-off. Maternal outcomes showed 2.9 folds increased risk for preterm delivery with the 1-hour OGTT of >180 mg/dl ($P=0.021$) and 6.7 times likely to have gestational hypertension with the 2-hour OGTT of > 140 mg/dl ($P=0.011$).
Conclusion
It is recommended to utilize the IADPSG criteria, but the usage of 2 h OGTT of >140 mg/dl instead of >153 mg/dl showed added advantage for the Filipino population.

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P433

Ankle-brachial index values in diabetic patients with and without claudication

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Aim
The ankle-brachial index (ABI) shows the existence of peripheral arterial disease and is also related to cardiovascular mortality in diabetic patients, even in those with coronary artery disease at an early stage. Normal levels are considered to be an ABI of 0.9 – 1.3; ABI thresholds of less than 0.9 and more than 1.3 are highly suspicious for PAD and high CV risk in diabetic patients. In this study, we planned to investigate the ankle-brachial index values in diabetic patients with and without claudication.
Materials and methods
Hundred patients were enrolled in this study. 16 patients with coronary artery disease or cerebrovascular disease were excluded. All of 84 patients were underwent ankle-brachial index (ABI) measurements in the out-patient department of internal medicine.
Results
Forty-four patients with claudication and 40 patients without claudication were included in the study. We couldn't palpate tibial artery in three patients and dorsal artery in three patients. These six patients were reffered cardiovascular surgery due to complete obstruction. There was no significant difference between age, a1c, body mass index (BMI), waist circumference, duration of diabetes mellitus (DM) of these two groups. The right ABI was found to be higher in patients with claudiation (1.18 ± 0.19) than patients without claudication (1.06 ± 0.18) ($P=0.003$). Also the left ABI was found to be higher in patients with claudiation (1.11 ± 0.2) than patients without claudication (1.05 ± 0.18) (p: 0.012) (table 1). However, patients with normal and abnormal ABI levels (0.9-1.3) were not found to be related to claudication complaint. Cigarette, family history, antihypertensive drug, statin, metformin, sulfonylurea, dpp4, glitazone or insulin use were not found to be related with claudication complaint. There was a significant relationship between neuropathy ($P=0.023$), sex ($P=0.039$) and claudication complaint. In the analysis of correlation, left and right ABI measurements were not found to be correlated with age, a1c, BMI, duration of DM.
Conclusion
Early diagnosis of PAD in diabetic patients without coronary artery disease or cerebrovascular disease can be done with ABI measurments. It is especially important to take ABI measurement in our everyday practice for diabetic patients with neuropathy and claudication complaint before yet developed macrovascular complications.

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P434

Analysis of kidney biopsy findings in diabetic patients

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Kidney disease occurs in diabetic patients during disease course in time. Diabetes duration, co-morbid diseases, presence of retinopathy, family history of diabetic nephropathy (DN) predict kidney involvement. Although DN is the initial diagnosis in diabetics with proteinuria, other diseases like primary glomerulonephritis (GN) could be the reason of kidney involvement. DN is increasing in proportion with the increase in diabetes prevalence, and it has been predicted to continue to increase in the future. We aimed to analyze the biopsy findings of diabetic patients who presented with renal findings apart from DN.
Methods
The study included 47 (30 males, 17 females) diabetic patients who performed kidney biopsy between 2002 and 2016. Biopsy indications were atypical presentation, like hematuria, proteinuria without retinopathy, acceleration in proteinuria, and unexpected deterioration of kidney function.
Results
The mean age of patients was 56.2 ± 11 years, diabetes duration was 6 ± 4 years. Serum creatinine levels were 2.24 ± 1.6 mg/dL, albumin 3.16 ± 0.77 g/dL, urinary protein excretion 7.52 ± 6.9 g/day, HbA1C 6.0 ± 0.81%, CRP 2.83 ± 5.2 mg/dL, total cholesterol 242 ± 102 mg/dL, triglyceride 225 ± 101 mg/dL and LDL cholesterol 160 ± 92 mg/dL. The biopsy indications were nephrotic syndrome (74.5%), asymptomatic urinary abnormality (17%), rapidly progressive kidney disease (6.4%) and nephritic syndrome (2.1%). DN was diagnosed in 18 diabetic patients (38.3%). Others were focal segmental glomerulosclerosis in 5 patients, AA amyloidosis in 5, IgA nephropathy in 4, membranous GN in 3, AL amyloidosis in 3, ANCA-associated GN in 2, membranoproliferative GN in 1, post-infectious GN in 1, hypertensive nephrosclerosis in 1, thrombotic microangiopathy in 1 and nonspecific changes in 3. The patients were divided into two groups as DN and non-DN. There was no significant difference between characteristics of both groups. Only the ratio of diabetic retinopathy in DN group was higher than that of non-DN group (44 vs. 6.9%, $P=0.003$).
Conclusion
The present study suggests that non-diabetic kidney pathologies may be common in diabetic patients. Therefore, a kidney biopsy may be useful in diabetic patients with atypical presentation. Although diabetic retinopathy was found to be an important predictor for DN, it is not known whether it's presence can completely differentiate DN from non-diabetic etiologies.

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P435

Hypomagnesemia as a marker of diabetic nephropathy

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Magnesium is an essential element and has a fundamental role in carbohydrate metabolism in general and in the insulin action in particular. Magnesium is involved in multiple levels in insulin secretion, binding and activity. Cellular magnesium deficiency can alter the activity of the membrane bound Na + K + ATPase, which is involved in the maintenance of gradients of sodium and potassium and in glucose transport. Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes as well as on the evolution of complications such as retinopathy, arterial atherosclerosis and nephropathy. Moreover, low serum magnesium is a strong, independent predictor of development of type 2 diabetes. A cross sectional study included 105 type 2 diabetic patients. Twenty nine were males (27.6%) and seventy six were females (72.4%).Their ages ranged from 30 to 77 with a mean of 49.7 ± 10.6. All patients were subjected to full clinical examination, and investigations which included: serum creatinine, HbA1c, albumin creatinine ratio and serum magnesium. Their mean BMI was 23 kg/m^2 and mean waist/hip ratio was 0.9.Their mean HbA1c was 8.55%. Of all patients, 13 of them had normal level of A/C ratio (control group) and 92 were albuminuric with a mean A/C ratio 238.26 ± 727.9 with a range of 33.7 (0.09–4700), mean s.creatinine was 1.29 ± 1.16 and their mean s.magnesium level was 2.04 ± 0.49 with a range of 1.9 (0.8–3.9). We observed significant negative correlation between A/C ratio and serum creatinine with a P-value of <0.0001. The study shows negative correlation between serum magnesium and A/C ratio($r = -0.202$, $P = 0.039$).

Keywords: Type 2 diabetes, diabetic nephropathy, albuminura, hypomagnesemia.
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P436

Association cystatin C with the presence of carotid atherosclerosis in patients with diabetes type 2 and chronic kidney diseaseassociation cystatin C with the presence of carotid atherosclerosis in patients with diabetes type 2 and chronic kidney disease

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Objective
Cystatin C has been proposed as a novel marker of renal function and as a predictor of the severity of coronary atherosclerosis and future cardiovascular events. The aim was to evaluate the possible role of chronic kidney disease and particularly CysC on the characteristics of carotid atherosclerosis in patients with type 2 diabetes (DT2).
Materials and methods
We investigated 195 patients both sexes with DT2 aged 56.54 ± 4.17 years. Control group included 84 healthy subjects the same age. The intima-media thickness (IMT) was measured as the distance between the lumen-intima interface and the media-adventitia interface. Atherosclerotic plaque was defined as a focal structure encroaching into the arterial lumen of 0.5 mm or 50% of the surrounding IMT value. Total plaque area (TPA) was calculated as the sum of all plaque areas. GFR was estimated using the modification of diet in renal disease (MDRD) equation.
Results
Patients were divided into 2 groups by CysC levels tertiles. Patients in the high CysC tertile ($n = 76$) had significantly higher mean carotid IMT (0.88 ± 0.12 mm vs. 0.76 ± 0.07 mm, $P = 0.03$), and TPA (4.69 ± 2.03 mm^2 vs. 2.71 ± 0.57 mm^2, $P = 0.02$) compared to patients in the lower tertiles ($n = 119$). CysC levels demonstrated significant positive correlation with the mean carotid IMT ($r = 0.35$, $P = 0.011$). In multivariate analyses adjusted for cardiovascular risk factors, the association between CysC and IMT remained significant ($P = 0.037$). In contrast, neither serum creatinine nor estimated GFR were associated with IMT ($P = 0.17$).
Conclusions
Our study demonstrated a significant association of increased CysC levels with characteristics of carotid atherosclerosis in patients with type 2 diabetes and chronic kidney disease.

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P437

Diabetic ketoacidosis among SGLT2i-treated patients: insight from a single medical center located in the region with the highest diabetes mellitus mortality rate in Israel

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SGLT2i drugs have been funded by the Israeli health basket since 2017 for patients with type-2-diabetes and previous cardiovascular disease, as a result of the EMPA-REG outcome studies documenting 34% reduction in all-cause mortality. In 2015 the FDA warned that SGLT2i may result in diabetic-ketoacidosis (DKA). The reported DKA cases were not typical because many had type-2-diabetes and their blood glucose was slightly increased.
Objective
To describe DKA cases among patients treated with SGLT2i hospitalized in the Hadera region.
Methods
The electronic files of all hospitalized patients with DKA diagnosis (codes 250.10-13) during 2015-2017 were reviewed. Patients on SGLT2i treatment were analyzed.
Results
No cases were documented in 2015, two in 2016 and nine in 2017. DKA diagnosis and treatment within the hospital was delayed in 2(18%), length of hospital stay was 5.3 ± 1.9 days, 10 (91%) were diagnosed in the community as type-2-diabetes. Antidiabetic treatment: insulin 7(64%), metformin 7(64%), DPP-IVi 5(45%), GLP-1 agonist 3(27%) and sulfonylureas 2(18%). Mean blood glucose was 280 ± 84. Precipitating factors: 2(18%) had infection, 1(9%) drinking alcohol, 6(86%) stopped insulin. Four (40%) had pre-hospitalization clinical signs suggestive of LADA, of these: 3 were insulin treated, and 2 had recurrent DKA. Severity score was: 2(18%)-mild, 4(36%)-moderate and 5(45%)-severe; one died. Two restarted SGLT2i treatment after hospitalization, one recurred with DKA.
Conclusion
Patients with obvious insulin deficiency are being treated with SGLT2i, including some with previous DKA. Community and the medical center physicians and nurses should be aware of the a-typical presentation of DKA among patients with diabetes and SGLT2i.

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P438

Investigation of serum SCUBE-1 level in relation to microvascular complications in patients with type 2 diabetes mellitus

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Objective
The aim of this study was to investigate the association between serum level of signal peptide-CUB-EGF domain-containing protein 1 (SCUBE-1) and both type 2 diabetes mellitus and its related microvascular complications.
Material and methods
The study was included 50 type 2 diabetic patients with complications (group 1), 50 diabetic patients without complications (group 2) and 50 healthy individuals as control group (group 3). Anthropometry and blood pressure measurements were performed in all participants. Serum SCUBE-1 level was measured by ELISA method. Blood levels of fasting glucose, BUN, creatinine, liver function tests, prothrombin time, active partial thromboplastin time, hemoglobin, platelet count, serum lipid parameters, and HbA1c values of participants were recorded. The diagnosis of diabetic retinopathy was performed by indirect fundus examination

following pupil dilatation. The diagnosis of diabetic nephropathy was determined by microalbuminuria that measured by a 24-hour urine collection.
Results
The groups were similar in terms of age and gender ($P>0.05$). The median SCUBE-1 serum levels were 5.2 (2.35–9.55) ng/ml, 3.68 (1.47–6.42) ng/ml, and 3.87 (2.13–6.69) ng/ml in group 1, group 2, and group 3, respectively ($P=0.365$). There was not any significant difference between the groups according to SCUBE-1 serum level if diabetic subjects were divided into two groups according to their HbA1c levels as >7% or <7% ($P=0.913$). When all subjects were divided into two groups according to their fasting blood glucose levels as <200mg/dl or >200 mg/dl, median serum SCUBE-1 levels were 3.57 (1.79–6.72) ng/ml and 5.63 (2.45–9.88) ng/ml, respectively ($P=0.030$).
Conclusion
There was a positive correlation between serum SCUBE-1 level and fasting blood glucose level. However, there was not any meaningful change between serum SCUBE-1 level and diabetic microvascular complications such as diabetic retinopathy or nephropathy.

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P439

Hyperlipidemia during gestational diabetes: maternal and offspring complications

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Lipid profile suffers adaptive changes during pregnancy due to estrogen stimulation and insulin resistance. Several relations have been suggested between maternal lipid profile, glucose tolerance, endothelial cell dysfunction and long-term cardiovascular risk; the effects of maternal lipid profile metabolism in fetal growth are also inconclusive. Since a regular evaluation and follow-up of lipid profile during pregnancy has not been stablished yet, we aimed to evaluate the incidence of dyslipidemia in patients with gestational diabetes (GDM) and analyze some putative relations with pregnancy, offspring complications and maternal metabolic syndrome parameters determined three and twelve months after delivery.
Patients and methods
Two hundred and fifty patients with GDM were included. Full medical history, offspring characteristics, lipid profile and maternal variables of metabolic syndrome were evaluated during pregnancy, three- and twelve-months after delivery, the incidence of dyslipidemia during pregnancy was determined using two different classifications.
Results
Lower plasma HDL and hypertriglyceridemia were the most current disorder; prematurity or birth weight were not correlated with dyslipidemia; during pregnancy the lipid-related parameter that better predicted the risk of offspring macrosomia was triglycerides (TG); high TG three months after delivery were correlated to macrosomia and metabolic syndrome characteristics before and after pregnancy (three and twelve months).
Conclusions
TG during pregnancy is the parameter that best predicts the risk of macrosomia and is related to increased metabolic risk after delivery, the evaluation of lipid profile and other metabolic variables during pregnancy and after delivery are required to early diagnose cardiovascular risk factors especially in high risk population.

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P440

Osteopontin levels in plasma, muscles and bone in patient with non-healing diabetic foot ulcers: a new player in wound healing process?

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Background
The present study was designed to investigate the impact of osteopontin (OPN) in different tissue (e.g., plasma, muscles and bone) on amputation rate (in-hospital and during one year follow-up) for non-healing diabetic foot ulcers (DFUs).
Methods
This pilot study consisted of 30 diabetic patients, hospitalized due to non-healing DFUs. Patients were divided into two groups: Group 1 included 14 patients who underwent limb-preserved debridement procedure; Group 2 included 16 subjects who underwent amputation. Additionally, the study participants were divided into two groups according reccurent amputation rate during 1 year follow-up.
Results
Plasma OPN was higher and bone OPN was lower in Group 2 compare to Group 1 ($P=0.016$ and $P=0.004$, respectively). In the logistic regression analysis, bone OPN emerged as a significant independent predictor of amputation (OR=0.042, 95% CI 0.003–0.699, $P=0.027$). Plasma OPN was also associated with amputation such that each unit increase in plasma OPN was associated with increase in odds of amputation of 17.7% (95% CI 0.997–1.388, $P=0.054$). The study participants were divided into two groups according amputation during 1 year follow-up: Group 1 included 11 patients who underwent amputation; Group 2 included 19 patients who did not need amputation at one year follow-up. Plasma OPN were higher and bone osteopontin was lower in Group 1than in Group 2. However, in GLM analysis bone OPN was marginally associated with one year amputation.
Conclusions
Decreased levels of OPN in bone and increased plasma OPN are independently associated with in-hospital amputation in patient with non-healing diabetic foot ulcers.

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P441

Impaired awareness of hypoglycaemia does not affect the prevalence of diabetes-related distress in people with diabetes type 1

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Objective
The aim of this study was to assess prevalence of impaired awareness of hypoglycaemia (IAH) by the Gold method in people with type 1 diabetes and to compare people with and with IAH regarding metabolic control.
Methods
In a cross-sectional study, we assessed IAH in 139 people with type 1 diabetes (54.1y, diabetes duration 24.0y, HbA1c 7.1%) attending the University outpatient department for endocrinology and metabolic diseases. IAH was assessed using the Gold method by asking the question "Do you know when your hypos are commencing?" while scoring on a Lickert scale from 1 ("always") to 7 ("never"). A Gold score ≥ 4 is considered as IAH.
Results
Impaired awareness of hypoglycaemia had 25.2% (n=35/139) of the participants. Individuals with IAH had a longer diabetes duration (56.5 ± 13.3 vs. 53.2 ± 14.4 years, $P=0.001$) and lower threshold of blood glucose level when noticing first symptoms of hypoglycaemia (3.0 ± 1.2 vs. 3.7 ± 0.6 mmol/l, $P=0.006$) than people with normal awareness. Furthermore, people with IAH had more episodes of hypoglycaemia without symptoms (1-3 events per month: 31.4 vs. 17.5%, 1-3 per week: 37.2 vs. 17.5%). We did not find a difference of PAID Score in patients with and without IAH had (score 19.1 vs. 17.8 out of 100). There were also no differences regarding number of non severe an severe hypoglycaemia, satisfaction of diabetes treatment social status and HbA1c (7.0% vs. 7.2%, $P=0.363$), in individuals with IAH compared to normal awareness.
Conclusions
One out of four individuals with type 1 diabetes showed IAH. Risk of hypoglycaemia without symptoms is higher in people with IAH despite HbA1c is comparable between patients with IAH and normal awareness. To reduce risk of hypoglycaemia, glucose targets should be adjusted in people with IAH.

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P442

The comparison of the fate of arteriovenous fistula in diabetic and non-diabetic recipients following kidneytransplantation

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Native arteriovenous fistula (AVF) represents the best vascular approach for chronic hemodialysis. It is difficult to create an AVF in diabetic hemodialysis patients due to atherosclerotic changes in the arteries. Although AVF becomes useless after a successful kidney transplant, there is no accepted policy for preserving or ligating AVF. The aim of this study was to compare the fate of AVFs in diabetic and non-diabetic patients after kidney transplantation.
Methods
The study included 129 (66 males, 63 females) consecutive kidney transplant recipients with AVF. Our cohort excluded patients with vascular access problems and/or permanent catheter placement prior to transplantation. The patients were divided into two groups: diabetics ($n=25$) and non-diabetics ($n=104$). Features and fates of AVF in both groups were evaluated.
Results
The female ratio, mean age and body mass index of diabetic patients were higher than those of non-diabetics (72% vs 43%, $P<0.01$; 51 ± 8 vs 44 ± 10 years, $P=0.004$ and 29.9 ± 5.1 vs 26.9 ± 7.8 kg/m^2, $P=0.001$, respectively). The renal replacement type, donor type, donor age, systolic and diastolic blood pressures, pulse beat and hemoglobin levels were comparable between two groups. The ratio of brachiocephalic AVF was higher in the diabetics (68% vs 43%, $P=0.017$). There was no significant difference between history of dialysis catheter (72% vs 86.5%) and the ratio of functioned AVF (36% vs 54.4%) in diabetic and non-diabetic groups, respectively. Symptoms and findings did not differ between two groups. The ratio of aneurysm in non-diabetic groups was higher (28.8% vs 8%, $P=0.030$). In both groups, cosmetic and esthetic concerns were not different. The ratio of steal syndrome was higher in diabetics (12% vs 2.9%, $P=0.052$). After transplantation, AVFs were closed in 6 diabetic patients and 31 non-diabetic patients ($P>0.05$). The causes of fistula closure were similar (infection in 7, pain in 4, edema in 9, cardiac in 13, own choice in 2 and aneurysm in 1 patient). The ratios of ejection fraction, left ventricular hypertrophy, pulmonary hypertension and valvular disease in the patients were similar in both groups. Mean serum creatinine levels in non-diabetics and diabetics were 1.33 ± 0.59 and 1.48 ± 0.65 mg/dl at the last visit, respectively ($P=0.139$).
Conclusion
Our study showed that the presence of diabetes mellitus did not significantly affect fistula-associated symptoms and findings, fistula fate and graft survival after kidney transplantation.

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TSH and adiponectin levels in patients with diabetic kidney disease after renal transplantation

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Aims
Diabetic nephropathy (DN) is a leading cause of chronic kidney disease (DKD). Various hormonal disturbances are not rare among DKD patients. Adipose tissue as an active endocrine organ with multiple metabolic effects may play an extra important role in hormonal disbalance during progressive kidney function decline. The purpose of the study was to investigate potential relationship between thyroid status and adiponectin levels in patients with type 1 diabetes (T1D) and DKD after renal transplantation (RT).
Materials and methods
We recruited 121 patients (43 m; 78 f; age 42.26 ± 11.670 yrs; duration of T1D 23.07 ± 9.95 yrs) with T1D. Hypertension was observed in 84(69.42%) patients, 62(51.24%) patients took ACE inhibitors. Dyslipidemia was found in 107(88.43%) patients, and only 34(28.10%) of them received statins. GFR was estimated by CKD-MDRD formula. Kidney injury was assessed using NGAL. All patients were divided into 2 groups: the group 1 comprised 105 patients at stages 2–4 of DKD (GFR 64.0[49.00; 75.00] ml/min); group 2–16 patients with DKD after renal transplantation (GFR 42.5[27.95; 51.15] ml/min). In group 1–21 patients received replacement therapy with levothyroxin, in group 2 only 1 (mean dosage 106.55 ± 37.84 mcg vs 25.00 mcg). Biochemical parameters, HbA1c, thyroid hormones, NGAL, adiponectin levels were measured. Nonparametric statistical methods were used. A P-value <0.05 was considered significant.
Results
Groups were matched by age, gender, HbA1c, diabetes duration, blood pressure, LDLc levels. Comparative analysis of patients in the subgroups revealed reliable differences in BMI ($P=0.028$), adiponectin ($P=0.034$), NGAL ($P=0.009$), TSH ($P=0.048$), AbTSH-R ($P=0.002$). Mean BMI in group 1(25.53[22.54; 28.74]) was higher than those after RT(23.17 [20.87; 24.71]). Adiponectin levels were higher in patients after RT(26.65[16.73; 69.31]) vs DKD(14.18[10.46; 23.60]). Mean TSH levels were higher in patients after RT(3.16[2.39; 4.41] vs 2.27[1.61; 3.55]). AbTSH-R were much lower in patients after RT(0.33 ± 0.08 vs 0.545[0.3; 1.21]). NGAL levels were significantly higher in patients after RT 3.49[3.27; 6.69] vs 0.88[0.48; 1.75]. Correlation of adiponectin and TSH was observed in group 2($r=0.812$). In patients after RT TSH levels correlate with BMI ($r=0.579$). In group 1 inverse correlations of adiponectin and BMI was revealed ($r=-0.273$).
Conclusion
Patients with T1D after RT have reliably higher levels of TSH and adiponectin than patients with stages 2–4 of DKD, which may represent deeper metabolic disorders than in patients before transplantation.

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P444

Knowledge and Attitudes of Trainee Doctors in the Management of DKA and Compliance with current Protocol in a large University Teaching Hospital

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Diabetic Ketoacidosis (DKA) is a diabetic emergency with associated morbidity and mortality. Current evidence supports a protocol-based approach to its management. Our survey was conducted in a tertiary university hospital, where patients with DKA are initially managed as part of unselected general medical take.
Objectives
To assess knowledge and confidence of trainee doctors in DKA management. To review adherence to DKA protocol and identify areas for future intervention and improvement.
Methods
Using diabetes consultation records, we identified 30 patients admitted with DKA to our hospital between October 2016 and October 2017. We audited adherence to the current DKA protocol. Concurrently, a survey was circulated to medical trainees to identify knowledge and attitudes towards DKA.
Results
Suboptimal compliance with DKA protocol was identified with respect to fluid resuscitation and adequate monitoring of potassium, with subsequent development of hypokalemia in eight patients. 33.33% of patients developed hypoglycaemia during intravenous insulin infusion, most commonly due to delayed cessation of fixed, weight-based doses of insulin infusion once ketonemia had resolved. 55 (29%) of medical trainees working in the hospital responded to our survey. 60% of respondees demonstrated poor knowledge of appropriate fluid resuscitation. 75% reported that checking potassium at the advised intervals was only achievable on wards where nursing staff perform phlebotomy. Only 45% of those surveyed recognised the need to switch to variable rate insulin when DKA resolved. Only 20% expressed confidence in performing the switch from IV to subcutaneous insulin.
Discussion
Fidelity to DKA protocols is often poor. Prior research on interventions to improve compliance is primarily from the ICU setting. We show that deviations mirror areas where physicians lack confidence. A multifactorial educational intervention has been proven to be effective at improving guideline compliance in DKA.

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The association between glycemic markers and variability with plasma adipocytokine levels and markers of endothelium dysfunction in women with pregestational diabetes mellitus

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Introduction
Pregnant women with pre-existing diabetes are at greater risk of perinatal morbidity and diabetic complications. Glycemic control is the greatest impotance for both mothers and infants due to the risk of congenital anomalies, perinatal mortality and significant morbidity in the short and long term. Continuous glucose monitoring system (CGMS) is a novel tool to assess 24-h glucose fluctuations. In pregestational diabetes, CGMS may have an important role for excellent glucose control and treatment adjustments in conjunction with other glycemic status markers. Aim of this study was to assess relationship between these glycemic markers and CGMS parameters and their correlations with adipocytokine visfatin, 8-isoprostane, a marker of oxidative stress, and endogenous NOS inhibitor - asymmetric dimethylarginine (ADMA).
Material and methods
Twenty pregnant women (mean age 32.2±5) with pregestational diabetes mellitus (14 with type 1DM, 6 with type 2 DM with history of diabetes for 9.5 years) who admitted to our gestational diabetes mellitus outpatient clinics, were included in this study. All patients used insulin during pregnancy. CGMS profiles for >5 day in the 32 week of gestation were compared with glycemic markers-HbA1c and 1,5-anhydro-D-glucitol (1,5-AG). Visfatin, 8-isoprostane and ADMA levels were determined by ELISA.
Results
Seven of patient were primipar and 6 of them give more than 3 births. BMI before pregnancy was 25.8±3.3 kg/m^2, weight gain during pregnancy was 12.3±5.1 kg. Mean values of HbA1c, 1,5-AG were 6.5±0.6 and 0.5±03 ng/ml respectively. The number of glycemic excursions were 16.2±7.3 which was consist of high (11.6±6) and low excurtions (4.5±3.5). Mean absolute difference percentage (MAD%) was 12.5±6.6. Mean levels of visfatin, 8-isoprostane and ADMA were 6.4±3.8 ng/ml, 463.4±120 ng/L and 0.53±0.06 µmol/l respectively. HbA1c, fructosamine and ADMA levels were not associated with glycemic markers or other cytokine levels. Visfatin levels were correlated with 1,5 AG ($r=0.979$, $P=0.000$). 8-isoprostane levels were inversely related to the lowest value in CGMS data ($r=-0.649$, $P=0.002$). There were no significant interactions between cytokines and MAD%, glycemic excurtions in CGMS.
Conclusion
Including 1,5-AG, glycemic markers do not reflect glycemic variability. CGMS can be used to assess hypoglycaemia and glucose variability in conjunction with HbA1c. It is also important for treatment adjustment in all patients with type1 diabetes and patients with type 2 diabetes treated with insulin therapy.

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Acoustic Radiation Force Impulse Elastography and Ultrasonographic Findings of Achilles Tendon in Patients with and without diabetic peripheral neuropathy: a cross-sectional study

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Diabetic foot is one of the most feared complication of diabetes. The tendons and ligaments' stiffness and elasticity are known to be altered in diabetic foot. Achilles tendon (AT) plays an important for foot biomechanics and the altered stiffness of AT may have a role in pathogenesis of diabetic foot. Determination of the early changes in AT may help to identify the risky patients for diabetic foot. Acoustic Radiation Force Impulse (ARFI) Elastography is an elastography measures the shear wave velocity (SWV) of the target region inside the region of interest without external compression. Here we aimed to evaluate the elastographic features of AT with ARFI in patients with and without diabetic neuropathy. Forty five patients with type 2 diabetes recruited from the outpatient clinics served as the study group and were divided in two subgroups according to presence of peripheral neuropathy. Those with peripheral neuropathy were defined as group I (22 patients) and those without peripheral neuropathy were defined as group II (23 patients) Thirty age-, gender-, and body mass index (BMI)-matched healthy individuals were served as controls. The middle portion of Achilles tendon which is nearly 2-6 cm proximal to the calcaneus insertion is chosen for both ultrasonographic and ARFI elastographic examination. There was no statistically significant difference between the groups in terms of gender, age, BMI, height, and weight. HbA1c levels and fasting plasma glucose were similar between group I and group II. Achilles tendon thicknesses (ATT) were similar between group I and II $P=0.991$). Both patient group's ATT were significantly higher than controls. (group I vs control $P=0.01$; group II vs control $P=0.006$). Stiffness of AT as represented as SWV was similar between patients without neruopathy and control group ($P=0.993$). SWV was significantly lower in patients with neuropathy compared with patients without neuropathy and control group ($P<0.001$).

	Group I	Group II	Control Group
SVW of right AT (m/s)	4.0±1.1	5.4±1.0	5.4±1.1
SVW of left AT (m/s)	4.0±1.1	5.5±1.1	5.4±1.2

To the best of our knowledge this is the first study evaluating stiffness of AT with ARFI. In conclusion diabetic patients with neuropathy have thicker and softer AT however elasticity of AT of diabetic patients without neuropathy was similar with healthy controls. Softening of AT may be an early sign of diabetic foot and may indicate risky patients for diabetic foot.

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Impact of systemic and local cytokine status in diabetic foot syndrome on ulcers healing rate

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Aim
To study the relationship of cytokines level in patients with diabetic foot syndrome (SDS) with a healing rate of ulcerative defect and diabetes compensation.
Materials and methods
Twenty-four patients with DFS (DFS group) and 24 diabetic patients without foot ulcers (control group) (both groups comparable in age and other clinical and general laboratory characteristics, ongoing treatment, offloading mode). All DFS patients had chronic non-infected foot ulcers Wagner 2. Cytokine levels (IL-6,8,1,4) in the blood serum (both groups) and ulcers exudate (DFS group) were determined. Ulcer area was calculated at the first visit and in 8 weeks (if not healed).
Results
In the DFS group IL-1 and IL-6 level was significantly higher than in the control group – 94.53±3.2 vs. 34.95±1.36 and 16.33±1.02 vs. 9.27±0.27 ($P<0.05$) accordingly. In the DFS group IL-8 level in ulcer exudate was much higher than in the blood serum 35.56±2.5 vs. 9.76±1.84 ($P<0.05$). The correlation analysis revealed positive correlation between HbA1c and serum IL-1 ($r=0.634$, $P<0.05$) and IL-6 ($r=0.521$, $P<0.05$) level and IL-8 level in ulcers exudate ($r=0.654$, $P<0.05$) in the DFS group. Significant negative correlation was revealed between IL-4 level in ulcer exudate and wound healing rate in DFS group ($r=-0.620$, $P<0.05$) but no such correlation was revealed for HbA1c level.
Conclusion
Thus, the study of the local cytokine status (in ulcer exudate) in patients with DFS can help to identify new mechanisms that determine ulceration, limit and predict the course of the wound healing process.

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The relationship between cardiovascular autonomic neuropathy and the severity of coronary atherosclerosis

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Introduction
Cardiovascular autonomic neuropathy (CAN) is a significant risk factor for cardiovascular morbidity and mortality in patients with diabetes mellitus. However, an association between CAN and severity of coronary atherosclerosis in patients with ischemic heart disease (IHD) was not investigated.
Objectives
The aim of this study was to investigate the relationship of CAN and coronary stenosis in patients with clinical signs of IHD.
Materials and methods
We examined 63 patients, 48 men and 15 women with clinical symptoms of IHD (aged 61.79 ± 1.18 years, BMI – 30.39 ± 0.61 kg/m^2) (data are presented everywhere as mean ± SEM). All patients were performed coronaroventriculography, oral glucose tolerance test and 5 standart tests to diagnose CAN by Ewing. The diagnosis of CAN was confirmed in patients with 3 positive tests. The data analysis by SPSS statistical package version 23.0 for Windows.
Results
CAN was diagnosed in 52.4% patients, diabetes mellitus type 2 was diagnosed in 17.5% patients. All patients were divided for 3 groups depending on the number of occluded coronary arteries – with lesions in 1, 2 or 3 arteries. We found positive correlation between the number of the coronary arteries with atherosclerotic lesions and impaired results of Valsalva maneuver reflecting parasympathetic dysfunction ($OR = -0.27$, $P < 0.05$) and with the changes of diastolic blood pressure to isometric exercise (handgrip test) reflecting sympathetic dysfunction ($OR = -0.44$, $P < 0.05$).
Conclusion
We found some relationship between the severity of coronary arteries stenosis and sympathetic and parasympathetic dysfunction in patients with IHD with and without diabetes mellitus. These data can suggest the pathogenetic role of the impairment of cardiovascular autonomic regulation in the progression of atherosclerosis of coronary arteries.

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Type 1 diabetes is associated with a differential pattern of carotid atherosclerotic plaque types

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Introduction
The presence and type of atherosclerotic plaque is associated with future cardiovascular events (CVE). We previously described that increased frequency of plaques is associated with specific features in type 1 diabetes. The aim of the present study was to investigate the characteristics of atherosclerotic plaques in patients with type 1 diabetes mellitus (T1D).
Methods
A cross-sectional study of 174 subjects with carotid atherosclerotic plaques (46.6% women; mean age 53.6 ± 9.6 years; 107 with T1D, 61.5%) with normal renal function, and without history of CVE. All patients underwent: 1) carotid ultrasound (mode B) to assess the type of plaque, 2) collection of clinical variables.
Results
There was a differential pattern of atherosclerotic plaque types in patients with T1D compared with non-diabetic controls ($P = 0.001$): hypoechoic 48.6% vs. 73.1%; hyperechoic 25.2% vs. 7.5%; hypoechoic/hyperechoic 16.8% vs. 17.9%, and calcified with or without other plaque types 9.4% vs. 1.5%, respectively. In addition, hyperechoic plaques were more frequent in T1D compared to non-diabetic controls (49.5% vs. 26.9% $P = 0.005$). In the multivariate analysis, the risk of having a hyperechoic plaque was higher in T1D subjects (OR 2.64; $P = 0.008$), and lower the higher the creatinine value (OR 0.04, $P = 0.029$), and also in female subjects (OR 0.33, $P = 0.019$). There was a significant interaction between sex and age, with age being a risk factor only in men ($OR = 1.12$, $P < 0.001$).
Conclusions
Patients with T1D show a differential pattern of atherosclerotic plaque type, with a higher frequency of hyperechoic and calcified plaques than in non-diabetic subjects.

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Neurosensorial hearing loss in type 2 diabetic patients

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Introduction
There is a connection between neurosensorial hearing loss and tipe 2 diabetes. Diabetes is a systemic chronic disease that affects the vessels and nerves. There are 415 million people all over the world that suffer from diabetes. There is not a clear mechanism of how diabetes is related to hearing loss but it s possible that the high blood glucose levels associated with diabetes cause damage to the small blood vessels in the inner ear, similar to the way in wich diabetes can damage the eyes and the kidneys.
Aim
The role of tipe 2 diabetes in neurosensorial hearing loss in patient without any other systemic disease like HTA and without any other risk of hearing loss like loud noise proffesions, genetics, asthma and other chronic diseases of the middle ear: chronic otitis media, otosclerosis. Obtaining a normal glucose level in diabetic patients (HbA1C < 7%) prevents early RNS hearing loss.
Method and patients
We have taken in our study 2 groups: one group of 100 patients with tipe 2 diabetes without any other systemic diseases and the other is the control group of 100 healthy people from 45–65 years old, from 2015–2017. We performed: blood count cells, biochemical balance, HbA1c, urine test from the endocrinologist and otoscopy, audiometry, tympanometry from the ent doctor
Results
The average of HbA1C was 9.2%. Some of them had other diabetic complications such as diabetic nephropathy, retinopathy and neuropathy. We found normal otoscopy and tympanometry, bilateral RNS hearing in the higher tones in 60 patients, in wich in those with higher HbA1C with grave RNS hearing loss and in the others with medial RNS hearing loss.
Conclusions
There is a strong connection between poor control diabetes and RNS hearing loss. In those with grave RNS hearing loss it was irreversible and needed acoustic prosthesis. We recommended good control of diabetes and performe an audiograme in every patient detected with diabetes.

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Serum level of the autophagy biomarker beclin-1 in patients with diabetic nephropathy

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Introduction
Autophagy is a major clearance mechanism that destroys organelles and damaged proteins to keep cellular survival and homeostasis. Previous experimental studies have showed that autophagy has crucial role in the progression of diabetes and kidney diseases.
Aim
This pilot cross-sectional study aimed to investigate the association between serum concentrations of beclin-1, a key regulator of autophagy, and diabetic nephropathy.
Methods
The study included 70 patients with type 2 diabetes and diabetic nephropathy (group 1; 35 patients with eGFR > 30 ml/min/1.73 m^2 and group 2; 35 patients with with eGFR < 30 ml/min/1.73 m^2) and 20 age- and sex-matched healthy subjects as controls. Laboratory work up included; glycated hemoglobin (HbA1c), serum creatinine, estimated glomerular filtration rate (eGFR) using modification

of diet in renal disease (MDRD) formula, urine albumin to creatinine ratio (ACR), and serum beclin-1 measurement using an enzyme-linked immunosorbent assay.
Results
Patients with DN had significantly lower beclin-1 levels (2.38 ± 1.46 ng/mL) compared with control group (6.03 ± 1.94 ng/mL; $P < 0.001$). Moreover, patients in group 1 had significantly higher beclin-1 level (3.36 ± 1.30 ng/mL) than group 2 (1.43 ± .83 ng/mL; $P < 0.001$). In univariate analysis, the concentration of beclin-1 correlated well with eGFR ($r = .64$, $P < 0.001$), ACR ($r = -.63$, $P < 0.001$),and duration of diabetes ($r = -0.43$, $P < 0.001$) but didn't correlate HbA1c ($r = -.17$, $P = .15$).
Conclusion
This data suggest that low levels of serum beclin-1 could be a biomarker of DN in type 2 diabetic patients. Furthermore, it correlates well with the indicators of kidney function and renal damage.

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The comparison of longevity of arteriovenous fistula in hemodialysis patients with or without diabetes mellitus

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Vascular access remains both a life line and a 'weak link for patients receiving hemodialysis (HD) therapy. It difficult to create an arteriovenous fistula (AVF) in diabetic hemodialysis patients due to atherosclerotic changes in arteries. This study investigated the fate of AVFs in diabetic and non-diabetic HD patients.
Methods
The study included 306 patients (142 females, 164 males) on regular HD treatment with AVF. We excluded patients dialyzed with permanent catheter placement or arteriovenous graft. The patients were divided into two groups: diabetics ($n = 131$, 66 females) and non-diabetics ($n = 175$, 76 females). The history of cardiovascular diseases and AVF survival were evaluated.
Results
The dialysis features of both groups were comparable. The mean age and body mass index of diabetic patients were higher than those of non-diabetics (64 ± 10 vs 60 ± 15 years, $P < 0.014$, and 27.8 ± 5.3 vs 24.2 ± 4.1 kg/m^2, $P < 0.001$, respectively). There was no significant difference between the ratios of smoking and dyslipidemia in diabetic and non-diabetic groups (16.8% vs 21.7% and 7.6% vs 5.1%, respectively, $P > 0.05$). The ratios of coronary artery, peripheral and cerebral artery diseases were higher in diabetic patients than non-diabetics (6.2% vs 18.3%, $P = 0.002$; 2.3% vs 7.6%, $P = 0.049$; 2.1% vs 7%, $P = 0.004$, respectively). The longevity of AVFs was 26 months (range 0-1349) in diabetics and 30 months (range 0–-294) in non-diabetics ($P = 0.334$). The ratios of nonfunctioned AVF in diabetic group did not differ from non-diabetic group (26.7% vs 20.6%, $P = 0.220$).
Conclusion
Inadequate arterial inflow in diabetic HD patients have been increasingly recognized as the major cause of fistular malfunction. However, our study showed that the presence of diabetes mellitus in HD patients did not adversely affect longevity of AVF despite increased prevalence of arterial disease.

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Endothelial dysfunction in the diabetic foot

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Endothelial dysfunction (ED) is common in type 2 diabetes mellitus (T2DM) and can lead to microvascular and macrovascular complications. The aim of our study was to assess ED in patients with T2DM ($n = 21$; 13 with diabetic neuropathy (DN), 8 without DN) and compare them with non-diabetic controls ($n = 10$).
Methods
ED was assessed by skin microcirculation (SM) and biochemical markers (BM) of endothelial function. SM was measured on the dorsum of the foot by laser Doppler (LD) iontophoresis using the Perimed Laser Doppler Imager. Endothelial-mediated vasodilation (EMV) was measured by the iontophoresis of acetylcholine (Ach), while sodium nitroprusside (SNP) was used to study endothelium-independent vasodilation (EIV). Fasting blood samples were collected at baseline for markers of endothelial activation (ICAM, VCAM and inflammatory molecules like IL-6).
Results
Patients in the control group were younger and had lower BMI and HbA1c. There was no difference in skin microcirculation between groups, for both EMV and EIV. There was also no difference in biochemical markers of ED including ICAM, VCAM, however, there was a significant up-regulation of IL-6 in T2DM ($P = 0.006$)
Conclusions
In this small study we found no difference in skin microcirculation and biochemical markers of ED. Of note, the inflammatory marker IL-6 was raised in diabetic patients and whether this influences the endothelial dysfunction observed in this patient group remains to be corroborated in larger studies.

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Polyglandular Autoimmune Syndrome Type III(PAS) onset with diabetic ketosis caused by the insulin analog induced anti-insulin antibody: successful treatment with human insulin

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Type III PAS is defined as autoimmune thyroiditis occurs with another organ-specific autoimmune disease. Further PAS IIIA is subclassified as autoimmune thyroiditis with immune-mediated diabetes mellitus. Circulating organ-specific autoantibodies can be detected in these patients. We report a patient with Hashimoto Thyroiditis since five years on levothyroxine treatment with normal TSH levels and new onset insulin dependent Type I DM for 3 months. The patient was admitted Recurrent Diabetic Ketosis and succesfully treated by switching Analog insulin to Human Insulin. Analog–insulin Induced Anti-InsulinAntibody was thought to be the cause. 43-year-old female patient admitted to our hospital with diabetic ketoacidosis. She was treated with four times daily insulin injections with insulin aspart before meals and insulin detemir at bedtime. She did not miss any dose or there were no identified underlying cause for ketosis. She weighed 48.3 kg with BMI: 20.63 kg/m^2 and physical examination revealed no pathologic findings. Laboratory evaluation showed markedly increased HbA1c (10,5) levels together with decreased C-peptide levels (0.51 ng/ml). An autoimmunity screening was performed: antiGAD (51.27 IU/ml) and antiICA(+1) have positive results as suggesting the Type I DM. We started to insulin infusion with reguler insulin untill plasma ketones were negative. Insulin detemir and aspart were initiated as intensive treatment. Dose titration performed according to 7 point daily glucose monitorisation for a week. She has been treated with five daily insulin injections: 75 units of aspart and 60 units of detemir daily. Nevertheless her blood glucose levels were 200–310 mg/dl with this treatment. Consequently we started to insulin infusion with reguler insulin again. In the first hours of the regular infusion hypoglycemia developed with 4units/hour dosage. Anti-insulin antibody level was markedly elevated. (15U/ml; normal, <10 U/ml). We switched the treatment to regular and NPH insulin. Afterwards, her blood glucose quickly normalized and daily insulin need was decreased significantly to 50–55 units. She was discharged with regular insulin and NPH treatment. HbA1c level was 7.5% on third month follow-up. Immunological insulin resistance, which is characterized by a requirement for an insulin dosage over 120 U/day due to anti-insulin antibodies has since become quite rare. In the few reported cases, patients were treated with glucocorticoids or plasmapheresis Recently we succesfully treated a patient with severe immunological insulin resistance due to antibodies by modification of insulin administration; Analog insulin to Human Insulin.

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Bone markers and bone integrity in type 2 diabetes

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Type 2 diabetes mellitus (T2DM) and obesity are linked to osteoporosis, making these patients at increased risk of developing fractures. In this study we aimed to investigate bone biochemical markers and bone structure in diabetic patients to compare with non-diabetic controls.
Methods
We recruited 21 type 2 diabetic patients and 10 non-diabetic controls. Fasting blood samples were collected for markers of bone turnover (Sclerostin (SCL), RANKL, OPG, OPN, OCN, BMP4 and TGF-1β and the inflammatory marker IL-6. Calcaneal bone mineral density (BMD) was measured using a quantitative ultrasound device called Sahara Clinical Bone Sonometer, in which the bare heel is placed in the device and the BMD is calculated within 30 seconds and where the *T*-score, projected by the device, was used as an indicator of calcaneal BMD.
Results
Patients in the control group were younger and had lower BMI and HbA1c. There was no difference in BMD between groups. OCN was higher in control group, whereas SCL, OPG and IL-6 were raised in the type 2 diabetic group. Furthermore, the type 2 diabetic cohort showed a strong positive correlation between Sclerostin and OPG and IL-6 and RANKL; and a negative correlation between RANKL and OCN and IL-6 and BMP-4.
Conclusions
Fracture risk in diabetes may be mediated by modulation of bone-related proteins. Although BMD showed no difference in bone structure between diabetic patients and controls, the alteration detected in osteogenic factors could reflect the increased risk of vascular calcification present in diabetic patients. This will be investigated in future studies.

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Levels of scerostostin in serum and femoral vascular tissue and its relationship with atherosclerosis and cardiovascular mortality in patients with and without type 2 diabetes

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Introduction
Sclerostin is a glycoprotein expressed mainly by osteocytes, which acts as inhibitor of bone formation. However, several studies have shown an increase in serum levels of sclerostin in subjects with type 2 diabetes (T2D) and cardiovascular disease (CVD) suggesting an additional role of this protein at the vascular level. The hypothesis that sclerostin could be expressed by vascular smooth muscle cells (VSMCs) under calcifying conditions could justify this elevation. However, there are few data at the tissue level.
Objectives
Determination of serum sclerostin levels in non-diabetic and T2D subjects with CVD and a at the transcriptional and immunohistochemical levels in femoral vascular tissue of patients with DM2 with atherosclerosis and non-atherosclerotic vascular tissue from healthy controls. Evaluation of the relationship between circulating sclerostin levels and cardiovascular mortality in subjects with and without T2D.
Material and methods
Serum sclerostin levels were determined in 75 T2D subjects with and without CVD and in 55 non-diabetic controls by commercial ELISA kit (Biomedica). Sclerostin expression was determined by RT-qPCR from 400 ng of total RNA from 45 sections of atherosclerotic femoral arterial tissue from subjects with T2D as well as from a healthy control. The gene expression was normalized according to the expression of two constitutive genes (GAPDH and ubiquitin). Immunohistochemical detection of sclerostin was performed on sections of paraffined vascular tissue using 1:50 antiesclerostin-specific antibody (Sigma Aldrich) and chromogenic detection. The relationship between sclerostin and cardiovascular mortality was assessed by a competitive risk analysis (Fine & Gray) after the 7-year follow-up of the cohort of diabetic and non-diabetic subjects with and without CVD.
Results
Serum sclerostin levels were significantly higher in T2D subjects with CVD compared to controls (58.29 ± 26.36 vs 39.27 ± 12.71 pmol/l, $P < 0.001$). Increased expression of sclerostin at the transcriptional and immunohistochemical level was observed in atherosclerotic femoral artery of T2D patients compared with the femoral artery of healthy control. Serum sclerostin levels were independently associated with cardiovascular mortality ($P = 0.008$).
Conclusions
The increase in serum sclerostin associated with CVD in T2D could be associated with an increased expression of this protein by vascular tissue. This suggests the involvement of sclerostin in the atherosclerotic process. In addition, high levels of sclerostin are associated with increased cardiovascular mortality, and it could act as new biomarker of cardiovascular mortality risk.

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Serum lipid changes during pregnancy and after delivery in women with previous gestational diabetes

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Background
Women with a history of gestational diabetes mellitus (GDM) are at increased risk for diabetes and lipid alterations.
Objective
In a cohort of women with previous GDM, we aimed to ascertain whether women with abnormal glucose tolerance one year post-delivery had a more atherogenic lipid profile after pregnancy than those with normal glucose tolerance.
Design and patients
A descriptive study of GDM women who underwent pre and postnatal follow-up at the Hospital del Mar, Barcelona between January 2004 and March 2016 was conducted.
Results
Three hundred and six (56.8%) of 537 women diagnosed of GDM during the studied period, attended a control visit during the first year after delivery. The incidence of type 2 diabetes mellitus (T2DM) and prediabetes in these patients was 5.2% and 36.6%, respectively. High-density lipoprotein (HDL) cholesterol remained significantly lower in women with T2DM (48 ± 11 mg/dl vs 59 ± 12 mg/dl; $P = 0.009$) and the prediabetes group (54 ± 13 mg/dl vs 59 ± 12 mg/dl; $P = 0.029$) at the first year postpartum than in those with normal glucose tolerance. Additionally, triglycerides were higher in the T2DM group compared with the normal glucose tolerance group (128 ± 60 mg/dl vs 89 ± 41 mg/dl; $P = 0.009$). There were no differences in LDL cholesterol levels within the three groups.
Conclusions
Women with previous GDM who develop T2DM or prediabetes one year post-delivery have lower HDL cholesterol concentrations than those with normal glucose tolerance. Moreover, those who develop T2DM have higher triglyceride concentrations than those with normal glucose tolerance.

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P458

The relationship between oxidative stress markers and carotis intima media thickness in patients with diabetic microvascular complications

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Aim
To investigate the relationship between oxidative stres markers and carotis intima media thickness in diabetic patients with microvascular complications.
Material and methods
112 patients with type 2 diabetes mellitus and 44 healthy control subjects were included in the study. The presence of diabetic retinopathy was investigated by ocular examination. Neurological examinations were performed for neuropathy. In addition, catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), malondialdehyde (MDA), nitric oxide (NO) and serum prolidase activity were measured for oxidative stress in the morning blood samples of all patients. Carotis intima media thickness (CIMT) was measured.
Results
Of the patients with type 2 diabetes mellitus, 80 (71.42%) had complications and 41 (28.58%) had no complications. When the groups were compared in terms of biochemical data; CRP levels in diabetic complication group were significantly higher than the other groups ($P<0.001$). Creatinine levels in diabetic complication group were significantly higher than the other groups ($P<0.001$). Protein levels in spot urine in diabetic complication group were significantly higher than the other groups ($P<0.001$). LDL levels in the diabetic complication group were significantly higher tham the others group ($P=0.018$). Triglyceride levels in the diabetic complication group were significantly higher than the others groups ($P<0.001$). There was no statistically significant difference between the groups in terms of TSH and fT4 levels. When the groups were compared in terms of oxidative stress markers; the antioxidant stress markers (CAT, SOD, GPx) were found to be lower in the diabetic complication group than the other groups ($P<0.001$, $P<0.001$, $P<0.001$, respectively), while oxidative stress markers (MDA and NO) were found to be higher in the diabetic complicated group. When the groups were compared in terms of CIMT; the CIMT was significantly higher in diabetic patients than in the healthy control group ($P<0.001$). There was statistically significant negative correlation between CIMK and antioxidant stress markers (CAT, SOD, GPx) while there was statistically significant positive correlation between CIMK and oxidant stress markers (MDA, NO).
Conclusion
In our study, serum oxidative stress parameters were found to be statistically significantly higher in diabetic patients with complications than the healthy control and diabetic patients without complications. Also we found there is positive correlation between carotis intima media thickness and oxidant stress markers.

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Predictors of perinatal complications in pregnant women with gestacional diabetes

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Background
Pregnant women with gestational diabetes (GD) have a higher risk of perinatal complication compared to women without. Nevertheless, in women with GD, predictors of perinatal complication are not well established. We aimed to compare, in women with GD, those with and without perinatal complications and to study predictors of perinatal complications in women with GD.
Methods
Retrospective study of pregnant women followed in the Endocrinology clinic of Centro Hospitalar de Trás-os-Montes e Alto Douro who had a childbirth in 2016. GD diabetes defined as fasting glycaemia $\geq$92 mg/dl in the first trimester or a 7g-OGTT at 24–28 weeks with at least one abnormal value ($\geq$92; $\geq$180 or $\geq$153 mg/dl at 0, 60 or 120 min, respectively). HbA1c used was the closest to the end of pregnancy available. Perinatal complications defined as a combination of preeclampsia, polyhydramnios, fetal macrosomia, preterm labour ($\leq$37 weeks), neonatal hypoglycemia, neonatal hyperbilirubinemia, neonatal distress respiratory syndrome, or trauma during delivery. We compared women with and without perinatal complications: χ^2 test, student t test and Mann Whitney U test. A multivariate logistic regression analysis was built to study predictors of perinatal complications.
Results
We studied 104 women, 27 with perinatal complications. Mean age was 34 years, 37.5% had a college degree. Mean body mass index before pregnancy was 26.2$\pm$5.3 kg/m^2 with a mean weight gain at the first appointment and at delivery of 8.2 kg and 11.1 kg, respectively. Median time between diagnosis and first appointment was 5 (3–9) weeks and the diagnosis of GD was made in the first trimester in 39.4%. Mean HbA1c was 5.2$\pm$0.4% and 44.2% needed treatment with metformin and/or insulin. Cesarean delivery rate was 37.5%. There were no significant differences between pregnant women with and without perinatal complications except in the birth weight that was lower in those with complications (2896$\pm$628 vs 3188$\pm$390; $P=0.03$). In the multivariate logistic regression analysis (variables included: age; college degree; time to fist appointment; GD diagnosed in the first trimester; metformin and/or insulin treatment, and HbA1c), only a college degree was an independent predictor of perinatal complications, OR 3.35 (95% IC: 1.23–9.12), $P=0.02$.
Conclusions
Pregnant women with GD with and without perinatal complications have similar social, anthropometric and clinical characteristics. The only variable associated with perinatal complications was having a college degree. Pregnant women with a college degree had more than three times the risk of perinatal complications.

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P460

Role of the lipid profile as a predictive factor in the development of diabetic retinopathy in patients with type 1 diabetes

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Introduction
Diabetic retinopathy (DR) is the most common microvascular complication in patients with type 1 diabetes (T1D), and the role of lipids in the development of this complication is still controversial. In this study we have analyzed the association between lipid levels at onset and during the follow-up and the subsequent development of DR.
Methods
The cohort consists of 1132 patients with T1D who were diagnosed in Navarra between 1/1/1990 and 12/21/2016. Information on their LDL-cholesterol, HDL-cholesterol and triglycerides levels was collected at onset and during the follow-up, and the diagnosis of DR was accomplished according to the criteria of the American Academy of Ophthalmology. The results were analyzed using Student-Fisher t test, univariate regression and Cox multivariate regression model.
Results
Comparing the group of patients with T1D who developed DR in relation to those who did not develop it, we observed significantly higher LDL-cholesterol at onset (117.0$\pm$60.5 mg/dl vs 109.0$\pm$45.8 mg/dl, $P=0.002$), higher triglycerides (90.5$\pm$67.8 mg/dl vs 79.0$\pm$60.0 mg/dl, $P=0.02$); and significantly lower HDL-cholesterol at onset (45.5$\pm$22.2 mg/dl vs 49.0$\pm$20.0 mg/dl, $P=0.05$). In the univariate analysis, adjusting for other factors such as age, gender, BMI, smoking habit, blood pressure, and HbA1c or C-peptide levels, we observed that LDL-cholesterol, triglycerides and HDL-cholesterol were significantly associated with the risk of DR throughout follow-up. The multivariate analysis confirmed the results observed in the univariate results in terms of triglycerides: an increase of 10 mg/dl in triglycerides during the follow-up raises the risk of developing DR by 2.9% (HR 1.029 (CI95%: 1.01–1.05), $P=0.003$). However, the association between HDL-cholesterol and DR in multivariate analysis was only marginally significant (HR 0.91 (CI95%: 0.83–1.00), $P=0.058$); and the association of LDL-cholesterol with DR development was not significant.
Conclusions
1) In patients with T1D, lipid profile at onset is a predictor of DR development; 2) high levels of triglycerides can be considered as a risk factor for development of DR in T1D.

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P461

Markers of nitrosative stress, angiogenesis and inflammation linked to severity of complications in type 1 diabetes

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Background
Hypoxia, oxidative stress and inflammation induced by hyperglycaemia are 'key players' in development of diabetic complications.
Aim
To analyze differences in levels of nitric oxide (NO) and its metabolites nitrate and nitrite (NO2/NO3) and well as angiopoietin 2 (Ang2) and neuropeptide Y (NPY) in patients with type 1 diabetes and different complications status; to analyze associations between these markers.
Methods
Samples of 315 of LatDiane study patients with type 1 diabetes duration more than 1 year were analyzed. Albuminuria was estimated *via* morning spot urine albumin/creatinine ratio. eGFR was calculated with CKD-EPI equation. Ang2 and NPY in serum were measured by for Luminex xMAP Technology and ELISA respectively. Added concentration of NO2/NO3 in serum and urine was measured by Griess reaction. Production of NO in the whole blood was detected by means of ESP spectroscopy of Fe-DETC-NO complex.
Results
NO2/NO3 in serum was higher and in urine - lower in patients with macroalbuminuria and ESRD compared to normo- and microalbuminuric patients (serum: 50.054 ± 38.00 μM vs 32.35 ± 22.41 μM, $P=0.02$; urine: 550.63 ± 550.77 μM vs 917.84 ± 813.19 μM, $P=0.018$). Similarly, patients with proliferative retinopathy had lower NO2/NO3 levels in urine compared to earlier stages of retinopathy (701.26 ± 620.04 μM vs 961.35 ± 848.79 μM; $P=0.02$). Significantly lower levels of NO2/NO3 in urine were found also in patients with diabetic polyneuropathy. Ang2 levels were higher in patients with macroalbuminuria/ESRD (1696.7 ± 1379.88 pg/ml vs 785.0 ± 450.7 pg/ml, $P=0.001$), proliferative retinopathy (1015 ± 845.28 pg/ml vs 808.68 ± 538.09 pg/ml, $P=0.017$), history if CVD (1381.38 ± 1256.51 pg/ml vs 823.36 ± 548 pg/ml, $P=0.000$) compared to patients without these determinants. Higher NPY levels were found in patients with macroalbuminuria and ESRD compared to normo- and microalbuminuric patients (19.91 ± 7.14 ng/ml vs 14.52 ± 7.57 ng/ml, $P=0.001$). NO, NO2/NO3 in urine and serum as well as Ang2 and NPY correlated with eGFR ($P<0.05$). Serum NPY correlated with blood NO and serum Ang2 levels ($P<0.05$).
Conclusions
Differences in levels of nitric oxide metabolites, Ang2 and NPY levels are observed in biological fluids of patients with different stages of diabetic complications. Data on association between these markers provide new knowledge about links between hypoxia, inflammation and oxidative stress in type 1 diabetes.

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P462

Nonalcoholic fatty liver disease in men with type 2 diabetes mellitus and androgen deficiency

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Background
Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver diseases, and the presence of type 2 diabetes mellitus (T2DM) increases its incidence up to 90%. To date, the effect of androgen deficiency in men with T2DM on the development of NAFLD has not been studied.
Aim
To assess the effect of the endogenous testosterone (T) level on the incidence of NAFLD in men with T2DM.
Materials and methods
The study included 50 men with T2DM (mean age 53.6 ± 5.9 years) who were divided into 2 groups: the 1st one included 20 patients with T level ≥ 12.1 nmol/l, the 2nd - 30 men with T level <12.1 nmol/l. Patients underwent clinical examinations, such as: assess of anthropometric data (weight, BMI, waist circumference (WC), hip circumference (HC)), evaluation of parameters of carbohydrate and lipid metabolism, liver transaminases, total T level, immunoreactive insulin (IRI) and leptin concentrations. Also, all patients underwent magnetic resonance imaging (MRI) of the liver by the Dickson method with a double gradient echo into the phase and antiphase to quantify the liver fat fraction (FF), which allowed to determine the presence and severity of NAFLD. For statistical data processing, the STATISTICA software package (StatSoft 10) was used. The statistical analysis was carried out using the Mann-Whitney U test, a critical significance level was taken to be $P<0.05$. For statistical data processing, the STATISTICA software package (StatSoft 10) was used.
Results
The severity of obesity according to BMI, WC, HC was significantly higher in patients of the 2nd group. This was accompanied by a significantly higher level of IRI by 30% ($P=0.049$) and twice higher leptin level ($P=0.0008$) in patients with androgen deficiency, compared to the control group. In addition, in the 2nd group, the level of ALT was significantly ($P=0.034$) higher by 25% compared to patients of group 1. In men with a low level of endogenous T, the liver fat fraction was significantly ($P=0.0002$) 2.5-fold higher than in men without androgen deficiency (10.96 (7.78; 14.44) vs 4.2 (2.25; 5.86)%). These findings demonstrate the higher severity of NAFLD in men with late onset hypogonadism compared to patients not having T deficiency.
Conclusion
T deficiency in men with T2DM promotes the development and aggravation of the already existing NAFLD.

Keywords: Testosterone, liver, diabetes mellitus

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P463

Influence of ethnicity on gestational diabetes mellitus in the center of Israel: a retrospective cohort study

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Aim
The aim of this study was to compare maternal and neonatal outcomes between Israeli Arab and Jewish women with GDM not controlled with lifestyle modification.
Methods
We conducted a retrospective cohort study of women with GDM who were not controlled with lifestyle modification and were followed and gave birth in a university affiliated medical center between 2005 and 2015.
Results
The study included 343 women, 45 (11.8%) of them Arabs. There were no differences in the baseline characteristics between the two ethnic groups including age, gravidity, parity or pre-pregnancy body mass index. There were 41.85% Jewish women with good glycemic control compared to 31.4% of the Arab women ($P=0.197$). A similar fraction gave birth by caesarian section or assisted labor (%17.8 of the Arab versus 15.1% of the Jewish women, $P=0.669$). There were no differences in composite outcome comprised of pre-eclampsia, caesarian section due to diabetes, macrosomia and neonatal hypoglycemia (68.9% for the Arabs vs. 62.4% for the Jewish women $P=0.42$).
Conclusions
Our study did not find differences in maternal and neonatal outcomes of Arab and Jewish population of women with GDM controlled with glucose lowering agents. These results are not consistent with previous published data. It is possible that the Arab population in our study shares comparable socioeconomic elements with the Jewish one and has access to similar medical care. Other possible explanation is a small sample size of this study.

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Subclinical atheromatous disease detection improves cardiovascular event prediction in chronic kidney disease with and without diabetes

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Background
Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in chronic kidney disease (CKD) patients with and without diabetes mellitus (DM). Traditional cardiovascular risk factors fail to fully account for the increase in cardiovascular risk in these patients. The NEFRONA study is a large, multicentre, prospective, observational study that evaluated atheromatous disease (AD) in the carotid and femoral territories in a large cohort of Spanish CKD patients without previous CVD.
Objectives
To analyse the prognostic value of subclinical AD in CKD patients with and without DM on the incidence of cardiovascular events (CVE).
Materials and methods
NEFRONA cohort data from CKD patients with DM ($n=698$) and without DM ($n=1747$) were analysed. Patients underwent baseline carotid and femoral ultrasound examinations and were followed-up for 4 years. All the CVE during the follow-up period were registered. Bivariate analysis and Fine-Gray competing risks models were used to perform the statistical analysis. Hazard ratios and 95% confidence intervals were reported.
Results
Among patients with DM, 96 CVE (13.75%) were reported during follow-up. Male gender, renal replacement therapy (RRT) and insulin treatment were more frequent in DM patients with CVE compared to those without CVE. Among CKD patients without DM, 107 CVE (6.12%) were reported. Being older, RRT and decreased serum concentrations of HDL-cholesterol were more frequent among non-DM patients with CVE. Presence of plaque, number of plaques and having more than two vascular territories affected with plaque at baseline were more frequent among CKD patients with CVE (with and without DM). Following competing risks models, the variable predicting CVE among CKD patients with DM was number of territories with plaque at baseline (1.78 (1.39, 2.28)). The variables predicting CVE in CKD patients without DM were age (1.03 (1.00, 1.05)), number of territories with plaque at baseline (1.86 (1.43, 2.42)) and serum concentrations of 25OH-vitaminD (0.96 (0.93, 0.99)).
Conclusion
Presence and burden of subclinical AD is the most potent factor to influence CVE in CKD patients with DM whereas, in CKD patients without DM, other risk factors such as age and decreased serum concentrations of 25OH-vitaminD are also associated with an increased risk of CVE. Early detection of subclinical AD and identification of AD burden through arterial ultrasound, performed at different vascular territories, could improve prediction of CVE in these patients.

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P465

Wrist and ankle measurements in patients with and without diabetes-related macrovascular disease

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Aim
We aimed to evaluate wrist and ankle measurements in patients with and without diabetes-related macrovascular disease.
Material and method
151 consecutive patients with type 2 diabetes who came to our diabetic outpatient clinic were included. We have divided the patients into two groups. Group 1 (patients with diabetes related macrovascular complications) and group 2 (patients without diabetes related macrovascular complications). Group 1 (*n*:45) includes diabetic patients with complete occlusion of one of the lower extremity arteries (right and left leg, dorsal and tibial arteries), cerebrovascular disease, coronary stenting, history of myocardial infarction (MI), coronary artery bypass graft (CABG) and diabetic foot. Group 2 (*n*:106) includes diabetic patients without macrovascular complications.
Results
In Group 1 there were 14 patients with complete occlusion of one of the lower extremity arteries, 10 patients with cerebrovascular disease, 20 patients with coronary stenting, 13 patients with history of myocardial infarction (MI), nine patients with coronary artery bypass graft (CABG) and one patient with right leg amputation due to diabetic foot disease. Wrist circumference was found to be statistically significantly thicker in group 1 (18.17 ± 1.46) than group 2 (17.53 ± 1.73) ($P=0.042$). Statistical analyzes with chi-square test revealed a significant relationship between the presence of macrovascular complications and sex ($P=0.003$) (odds ratio(OR) 2.891, 95% confidence interval (CI) 1.405–5.952), antihypertensive drug use ($P=0.0001$) (OR 12.553, 95% CI 4.191–37.596), statin use ($P=0.018$) (OR 2.426, 95% CI 1.156–5.093), metformin use ($P=0.008$) (OR 0.379, 95% CI 0.184–0.781), presence of diabetic foot (OR 7.714% 95% CI 0.780–76.259), presence of neuropathy ($P=0.035$) (OR 2.246, 95% CI 1.049–4.806). In the analysis of correlation, positive correlations were found between wrist circumference and age ($r=0.192$, $P=0.018$), height ($r=0.273$, $P=0.001$), weight ($r=0.388$, $P=0.0001$), body mass index (BMI) ($r=0.187$, $P=0.021$), waist circumference ($r=0.382$, $P=0.0001$), ankle circumference ($r=0.362$, $P=0.0001$. Positive correlations were found between ankle circumference and BMI ($R=0.331$; $P=0.0001$), waist circumference ($r=0.365$; $P=0.0001$), wirst circumference ($r=0.241$; $P=0.003$).
Conclusion
In diabetic patients, the relation between waist/hip ratio and macrovascular complications has been shown in many studies. In this sudy, we have demonstrated that the wrist is thicker in patients with diabetic-related macrovascular complications. This study shows that wrist circumference measurement in diabetic patients may be an important predictive anthropometric measurement for macrovasular complications as waist/hip ratio.

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P466

Prevalence and risk factors of diabetes in chronic viral hepatitis B and C: about a retrospective study

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Introduction
Carbohydrate metabolism disorders are common in chronic liver diseases, from glucose intolerance to proven diabetes. The presence of diabetes during chronic liver disease is a factor of poor prognosis. The purpose of our study is to assess the prevalence of diabetes in chronic hepatitis B and C and to determine the risk factors.
Patients and methods
This is a retrospective study that collects all cases of chronic hepatitis hospitalized in the Gastroenterology department from January to December 2016. The search for an association with diabetes or glucose intolerance has been carried out systematically.
Results
133 cases of chronic viral hepatitis have been identified. The origin is viral C ($N=102$) and viral B ($N=31$). The average age of patients was 59.25 (range 26–83 years) with a sex ratio of 0.7. The fibrosis stage evaluated by fibrotest or liver biopsy was as follows: F0 ($N=13$), F1 ($N=6$), F2 ($N=21$), F3 ($N=12$), F4 ($N=81$). 42.1% of patients were suffering from diabetes (56 patients). A metabolic syndrome was noted in 46 patients. Diabetes was anterior to the diagnosis of cirrhosis in 19 patients, after the diagnosis of cirrhosis in 14 patients. Both diagnoses were recognized simultaneously in 8 cases. Diabetes was significantly correlated with: age $>$ 50 years ($P=0.001$), fibrosis $>$ F3 ($P=0.005$) and the presence of a metabolic syndrome ($P<0.001$), mainly in case of viral hepatitis C. In patients who received antiviral treatment, diabetes was a factor of poor therapeutic response ($P=0.03$).
Conclusion
In our series, the prevalence of diabetes in chronic viral hepatitis B and C is high and found in more than 40% of cases. Diabetes was associated with age >50 years, fibrosis $>$ F3 and the presence of a metabolic syndrome, mainly with viral hepatitis C.

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Hypoglycemia in patients with type 2 diabetes mellitus in geriatric population

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Introduction
Hypoglycemia is a complication of diabetes mellitus (DM) with high morbidity and mortality. Risk of hypoglycemia is affected by the type and duration of DM, use of insulin or oral antidiabetic agents, dietary habits and comorbidities. In this study, we aimed to understand frequency and causes of hypoglycemia in patients with type 2 DM in Turkish population and especially collect data about hypoglycemia in geriatric population.
Methods
Between May and August 2017, one hundred and eigthy three patients who applied to Endocrinology and Metabolism and Geriatric Medicine Policlinics of Gazi University Faculty of Medicine were included in this study. These patients answered the questionnaire which had multiple choice questions about their hypoglycemia experiences. Also clinical information of these patients taken in last 3 months was achieved from digital archive.
Results
In this study, hypoglycemia frequency was 59.2% in non-geriatric population ($n=142$), and 46.3% in geriatric population ($n=41$). However, frequency of nocturnal hypoglycemia was 22.0% in geriatric population and 2.4% of this was severe; whereas, in non-geriatric patients, frequency of nocturnal hypoglycemia was 13.4% and none was severe. In geriatric patients who had duration of diabetes less than ten years, frequency of hypoglycemia was 23.5% and more than ten years was 62.5%. In 50.0% of geriatric patients who were on intensive insulin treatment had mild-moderate nocturnal hypoglycemia. Hypoglycemia frequency in non-geriatric patients with diabetic complications was 1.5%, but in geriatric patients it was 10.0%. 37.5% of geriatric patients with atherosclerotic heart disease were experiencing hypoglycemia and 12.5% of them were experiencing hypoglycemia every day.
Conclusion
In this study, hypoglycemia was detected in approximately half of the patients with type 2 DM and geriatric patients had more nocturnal hypoglycemia episodes. We should take measures for prevention of hypoglycemia and its detrimental effects especially in geriatric patients.
Keywords: Hypoglycemia, nocturnal hypoglycemia, geriatric population
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Predictors for low bone mineral density assessed with DXA and trabecular bone score in patients with diabetes mellitus

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Background
Diabetes mellitus is a metabolic disease associated with an increased risk of fracture, despite normal or increased bone mineral density (BMD), especially type 2 diabetes mellitus (T2DM). Trabecular bone score (TBS) is an imaging investigation that measures the grayscale variations on the lumbar spine performed on the DXA machine. The aim of this study was to evaluate the determinants associated with low BMD and TBS in patients with type 1 and type 2 diabetes mellitus.
Methods
We retrospectively analyzed 47 patients with T1DM and T2DM from our clinic between 2015 and 2017. The exclusion criteria were: absence of diabetes, secondary causes for diabetes and age <18 years. We divided the group by T/Z score and TBS and evaluated the predictors for bone structure. To identify the predictors, we performed binary logistic regression. In the multivariate analysis were introduced all the variable with $P<0.2$ in group comparison. Predictive performances of significant variables were evaluated.
Results
Among the 47 patients, 76.6% had a TBS compatible with altered bone structure, while only 31.9% had a T/Z score diagnostic for osteopenia or osteoporosis. The predominant gender was female (83%), median age was 63 years (IQR: 54–68) and the study group was characterized by overweight (mean BMI $=30.5\pm4.9$). The mean duration of DM was 10.9 ± 7.4 years. The majority of patients had type 2 DM (89.4%). By multivariate analysis, β-crosslaps (CTX) was independently associated with a low T/Z score (adjusted OR $=1.02$; 95% CI: 1.010–1.029, $P=0.001$). The cut-off value of CTX $=0.2915$ ng/ml had a sensitivity of 86.7% (95% CI: 59.54–98.34%), specificity of 78.1% (95% CI: 60.03–90.72%) and an AUC of 0.85 (95% CI: 0.72–0.98, $P<0.0001$) to predict osteopenia or osteoporosis. Also, in multivariate analysis age was independently associated with low TBS (adjusted OR $=1.08$, 95% CI: 1.01–1.14, $P=0.02$). The cut-off value of age of 61.5 years had the best predictive performance for altered bone structure, with a sensitivity of 69.4% (95% CI: 51.9–83.6%), a specificity of 72.7% (95% CI: 39–93.98%) and an AUC of 0.73 (95% CI: 0.54–0.91, $P=0.02$).
Conclusions
Patients with diabetes mellitus showed a more altered bone quality using TBS than DXA and β-crosslaps is an independent predictor for low BMD using DXA, while age is an independent predictor for low spine TBS.
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Is-it safe for diabetic patients to fast during Ramadan?

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Introduction
As Ramadan fasting is one of the five pillars of Islam, more than one billion muslims fast simultaneously worldwide. Patients with diabetes especially those with type 1 diabetes who fast during Ramadan, are at increased risk of diabetic ketoacidosis, particularly if their diabetes is poorly controlled before Ramadan. The aim of our study was to compare the incidences of diabetic Ketosis or ketoacidosis during in the month of Ramadan, the preceding month (Shaaban), and the following month (Shawal).
Methods
We performed a prospective study that included all known diabetic patients admitted with diabetic ketosis or ketoacidosis in the different departments of the National Nutrition Institute of Tunis during the pre-Ramadan month, Ramadan and post Ramadan month of 2 years 2015 and 2016. Demographics, clinical, and laboratory indices were collected.
Results
Total number of patients who were admitted with diabetic ketosis or ketoacidosis was 136 patients, 42 during Shaaban, 38 during Ramadan and 56 during Shaawal. There was no significant difference in the number of patients admitted with ketosis or keto acidosis during the three periods ($P=0.425$). The duration of acidosis during Ramadan (19 ± 24 h) was slightly higher than the others periods (17 ± 18 hours before and 15 ± 10 hours after) ($P=0.906$). During Ramadan, 58% of patients were with type 1 diabetes, 43% before Ramadan and 48% after Ramadan ($P=0.013$). The mean age of patients during Ramadan was significantly lower than during the two other periods ($P=0.027$). Non-compliance was the main precipitating factor during in the whole study periods.
Conclusion
Our study showed no significant difference in the incidence of ketosis or ketoacidosis during Ramadan compared to preceding and later months (Shaaban and Shaawal). Structured education seems to be important to avoid these diabetic complications during Ramadan.
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P470

Risk factors for delay gastric emptying in patients with type 2 diabites

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Introduction
The objective of the research was to determine the predictive value of the most probable etiopathogenetic factors contributing to the development and progression of gastric dysfunction in patients with type 2 diabetes. Only 5% of type 1 and 1% of type 2 diabetic combine the delay of gastric emptying (DGE) with typical gastroparesis symptoms. Systematic review of risk factors of development and progression symptoms of diabetic gastroparesis (DG). Results

presented from searches undertaken to ascertain predictors to early diagnostic of gastric dysfunction. It is associated with marked glycemic lability and it has significant morbidity.
Materials and methods
We have studied 170 patients with type 2 diabetes and disease duration of 10.3 ± 0.4 years; the patients' average age was 57.8 ± 0.9 years; there were 85 males and 85 females. The BMI – 33.1 ± 0.8 kg/m^2; the neurological symptoms score (NSS) – 18.1 ± 0.2 points; HbA_1C – 8.7 ± 0.2%, fasting glucose – 7.9 ± 0.4 mmol/l. The patients completed the gastroparesis cardinal symptom index (GCSI). To assess the severity of diabetic polyneuropathy (DPN) symptoms, a generally accepted scale measuring neurological symptoms and objective signs included into the NDS – the NSS was used. The stomach function was determined using the ^{13}C-octanoate breath test (^{13}C-OBT) No subjects studied have had the signs of other disorders of dysfunction in gastrointestinal motility.
Results
According to the questionnaire results, physical examination data as well as additional laboratory and instrumental investigations, mild DG was found in 17.7% subjects, moderate DG was observed in 19.3% patients and the signs of severe DGE were present in 8.0% patients only. Thus, the proportion of patients with gastric dysfunction among patients with diabetes was 45.0% which slightly exceeded the results of epidemiological studies. According to the linear regression analysis, in patients with type 2 diabetes, there was a positive correlation between the degree of DGE and the duration of the underlying medical condition, DPN manifestations, cigarette smoking and the severity of hypoglycemic episodes. The 95% confidence interval for the unstandardized B coefficient was as follows: the GCSI and the NDS RR = 0.83, 95% CI = 0.56–1.09, P = 0.000; whereas the ^{13}C-OBT and the NDS RR = 2.20, 95% CI = 1.13–3.27; P = 0.000.
Conclusions
Diabetes duration of more than 10 years, severe manifestations of DPN, the increase in the incidence of hypoglycemic episodes as well as smoking should be considered as major risk factors for DGE in patients with type 2 diabetes.

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P471

Clinical and laboratory predictors of positive renal effects of vildagliptin

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Accumulating facts show that incretin-modulating therapy could be beneficial in both glycemic control and nephroprotection in type 2 diabetes (DM2). Clinical evidence for nephroprotective potential of DPP-4 inhibitors is limited and predictive determinants are unknown. The study conducted with DM2 patients aimed to assess renal effects of vildagliptin addition and identify their clinical and laboratory predictors. The study enrolled 44 insulin-treated male and female type 2 diabetic patients, aged 49–70 years with satisfactory glycemic and blood pressure (BP) control, without overt chronic kidney disease, severe micro- and macrovascular diabetic complications, and non-diabetic renal impairment. Patients were randomized either to continue insulin therapy (control, n = 21), or to receive vildagliptin (50 mg/daily) added-on insulin therapy (Vgroup, n = 23). At baseline and after 6 months of treatment we assessed eGFR using serum creatinine (eGFRcr), cystatin C (eGFRcys), and both (eGFRcr-cys), and creatinine-adjusted urinary markers (albuminuria (UACR), and collagen type IV (uColIV). Groups were comparable on the basis of sex and age. A2 category of CKD was detected in 47.6% of control patients and in 52.2% – in Vgroup, P = 0.76. At baseline there were no significant differences in assessed parameters. In the control group none of them changed significantly after 6 months of the treatment. Patients from Vgroup demonstrated significant decrease in HbA1c, insulin requirement along with the frequency of hypoglycemic episodes. Significant reduction in diastolic BP, serum cystatin C and excretion of uColIV was documented in Vgroup as well as the increase of eGFRcys and eGFRcr-cys. Correlation analysis showed that neither changes of serum cystatin C, eGFRcys and eGFRcr-cys nor changes of uColIV in Vgroup were significantly related to the dynamics of HbA1c (r = −0.31, 0.21, 0.19, and 0.13, respectively, P > 0.05 each). We found inverse association between the changes of systolic BP and eGFRcr-cys (β = −0.47, R^2 = 0.22, R^2 = 0.02) suggesting that hemodynamic mechanisms at least partially contribute to vildagliptin renal action. Stepwise regression analysis showed that lower levels of baseline eGFRcys were independent predictors of both eGFRcys and eGFRcr-cys increase (β = −0.61, R^2 = 0.37, and β = −0.45, R^2 = 0.20, respectively, P < 0.05 each). Reduction of uColIV excretion was more pronounced in older patients (β = −0.74) with lower levels of diastolic BP (β = 0.57), R^2 = 0.46, P = 0.002. In conclusion, vildagliptin administration was associated with reduction of uColIV excretion along with the increase of eGFRcreat-cys and eGFRcys, independent of glycemic control. Older age and lower baseline values of diastolic BP were predictive of better uColIV-response in patients receiving vildagliptin.

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P472

An assessment of abnormal liver function tests in a cohort of unselected diabetic patients

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Introduction
The prevalence of abnormal liver function tests (LFTs) in the general population has been estimated to be 8.1–9.8%. Abnormal LFTs are common in diabetes although there are still few studies describing the exact prevalence. AST-to-platelet-ratio-index (APRI) and Fibrosis-4-score (FIB4) are scoring systems which can be used to estimate the degree of liver fibrosis. An APRI score > 1 has a sensitivity of 76% and a specificity of 72% for predicting cirrhosis while a score > 0.7 has a sensitivity of 77% and a specificity of 72% for predicting significant fibrosis. A FIB4 score > 3.25 has a 97% specificity and a positive predictive value of 65% for advanced fibrosis. A score < 1.45 has a negative predictive value of 90% for advanced fibrosis.
Aims/Background
The aim of this retrospective study was to evaluate the prevalence of abnormal LFTs in patients attending a tertiary referral centre with diabetes. We also aimed to calculate APRI and FIB4 scores in this population.
Method
Electronic records were used to review all patients with who had LFTs processed in 2016. APRI and FIB-4 scores were calculated for each patient where the required variables (age, AST, ALT, and platelet count) were available.
Results
1777 patients were included in the study, of whom 1077 were male and 700 were female. 212 had type 1, and 1565 type 2 diabetes (T2DM). 600 (33.76%) patients had at least one abnormal LFT. ALT was the most commonly elevated enzyme, 410 (23.1%) having an abnormal result. APRI and FIB4 scores could not be calculated in 734 (41.3%) patients, mostly due to unavailable platelet counts. Of the remaining 1043 (58.69%), 30 (2.88%, 30 = T2DM) had an APRI score > 0.7 while 17 (1.63%, 17 = T2DM) had a score ≥ 1. 265 (25.41%) had FIB4 ≥ 1.45 and < 3.25, and 18 (1.73%) patients had a score ≥ 3.25.
Conclusion
The results of this study demonstrate a high prevalence of raised LFTs in the diabetic population. ALT was the most commonly raised liver enzyme. A small but significant cohort of patients had APRI and FIB4 scores suggestive of cirrhosis and liver fibrosis, although the accuracy of these estimates will need to be histologically validated in diabetes. APRI and FIB-4 scores are potentially useful as routine screening tools for liver disease in diabetes in conjunction with history and clinical examination, but require addition of platelet count to the panel of routinely measured blood tests.

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P473

The effect of glutathione S-transferase M1 and T1 polymorphisms on ascorbic acid plasma levels in diabetic patients

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Introduction
Type 2 diabetes mellitus have been associated with excessive production of reactive oxygen species. Glutathione S-transferase (GST) polymorphisms result

in decreased or absent enzyme activity and altered oxidative stress. Meta-analyses have indicated that deletion of either GSTM1 or GSTT1 is associated with a significant increased risk of coronary heart disease. The aim of this study was to evaluated if ascorbic acid (AA) plasma levels differ by GST genotype in diabetic patients with and without angiopathy.
Methods
An observational analytical case-control study in 123 Caucasians type 2 diabetic patients was performed. GI - 65 diabetics with angiopathy, GII - 58 diabetics without angiopathy. Plasma levels of AA were measured by a validated HPLC method. The genotyping of GSTT1 and GSTM1 it was determined simultaneously by PCR-Multiplex technique.
Results
The frequency of GSTM1 and GSTT1 single-null genotypes was 42.9% and 30.8% in group I and 43.9% and 31.0% among in group II. The percentage of diabetics patients who had both GSTM1 and GSTT1 functional genotypes was GI:46.0% and GII:42.9%, who had one of the present genotypes was GI:33.4% and GII:37.5% and who had both null genotypes was GI:20.6% and GII:19.6%. Plasma AA concentrations were lower in those with the GSTT1 null genotype than in those with the GSTT1 functional genotype. GSTM1 null genotypes had higher plasma AA levels than those with functional GSTM1 allele. Suboptimal AA plasma concentrations (<4.93 µmol/L) were more frequent in GSTT1 deletion genotype (76.3%) compared to GSTT1-1 (69.4%). Inversely, the percentage of patients with functional GSTM1 allele (72.1%) was higher than null genotype (67.3%).
Conclusion
Plasmatic levels of AA differ by GSTM1 and GSTT1 polymorphisms in Caucasians diabetic patients with or without angiopathy. The upper and lower regulation of AA plasma levels in subjects with nonfunctional GSTT1 or GSTM1 could be partially understood to compensate the lack of functionality.

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P474

Maternofetal complications of diabetic pregnancy: about 293 cases

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Introduction
Pregnancy in women with diabetes is considered high risk because of potentially serious maternal and fetal complications that can put in to risk the maternal and fetal prognosis.
Objective
Describe and analyze risks associated with diabetic pregnancies and compare maternal fetal prognosis of pregnancies with pregestational diabetes (T1D and T2D) with gestational diabetes mellitus (GDM).
Patients and methods
It was a descriptive retrospective study including 293 diabetic pregnant women, hospitalized in Endocrinology and Diabetology department of Ibn Rochd University Hospital of Casablanca, over a period from January 2013 to December 2016. Data collection was done from medical records. The statistical analysis was done by SPSS.
Results
The middle-aged of patients was 31.6-year-old, 50.5% had T2D, 24.5% T1D and 25.5% had GDM. 38% of patients had a history of miscarriage, 20.3% fetal death in utero (FDIU) and 38% had macrosomia. Regarding maternal complications: 41.5% of patients delivered by Caesarean section which 30.6% had pregestational diabetes and 9.6% had GDM (p: 0.02), the threat of premature birth was 22%, 15% for preeclampsia, Urinary tract infection was significantly associated with patients with GDM ($P<0.001$) in the order of 22%. For fetal complications: 33% had macrosomia, 14.2%, neonatal jaundice, 9.5% were premature, polyhydramnios has been objectified in 13%, the FDIU in 16.2% of patients, neonatal mortality was of the order of 5.9%, 1.8% had shoulder dystocia and 6.3% of new borns were transferred to intensive care. Only macrosomia and shoulder dystocia were significantly associated with patients with GDM compared to those with pregestational diabetes (p: 0.008 and p: 0.001).
Discussion
We see a high rate of complications in diabetic pregnancies without prior followed with a high rate of miscarriages, fetal death, shoulder dystocia, and macrosomia, more frequent in cases of GDM.

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P475

Bacterial lower limb dermo-hypodermitisin diabetic patients: what epidemiological, clinical and therapeutic particularities? About 134 cases

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Introduction
The uncontrolled diabetics are led to develop severe infections like severe forms of acute bacterial dermo-hypodermitis. The aim of our study was to clarify the epidemiological, clinical and therapeutic characteristics of BDH in diabetic patients.
Patients and methods
A prospective, descriptive and analytical study was conducted in the Diabetology, Endocrinology and Metabolism Department, Ibn Rochd University Hospital of Casablanca, from January 2016 to December 2017, including all diabetic patients with BDH. Necrotizing fasciitis are excluded from the study. Statistical analysis was univariate for all the variables using SPSS version 22.0.0.
Result
Were included 134 diabetics, 57% had a T2D, their middle-aged was 53, and average HbA1c was 9.8%. 37% of patients were hypertensive, 32% dyslipidemic, 18% with ischemic cardiomyopathy, 37.5% had diabetic retinopathy, 61% diabetic nephropathy, 46% peripheral neuropathy and 23% autonomic neuropathy. Risk factors for BDH were a lower extremity edema in 38%, obesity in 30%, age greater than 65 years in 23%, inadequate hygiene in 22%, *obliterating arteriopathy of lower limbs* in 20%, active smoking in 16% and previous history of BDH in 11%. Average duration of consultation was 6 days. Localization was the leg in 67% of cases and the foot in 47%. Entry point was a fungal interdigital in 31% of cases, a perforating ulcer of the foot in 29%, and anarterial ulceration in 10%. BDH was accompanied by local signs of severity in 28% of cases, complicated in 14%. Fever was present in 43% of patients, with general signs in 37%. Infection was moderate involving the member in 34%, severe involving the lives of patients in 23%. Third-generation cephalosporins were used in 43% of cases, a monotherapy in 43% and dual therapy in 28%, initially, intravenously in all patients. Evolution was good in the majority of cases, 4 patients had presented a necrotizing fasciitis and 6 patients had presented a necrotizing bacterial dermo-hypodermitis without necrotizing fasciitis.
Conclusions
The diabetic is a subject at high risk of developing severe forms of BDH. Perforating ulcer of the foot and arterial ulceration are frequently the entry points.

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Diabetes Therapy

P476

Analysis of safety and efficacy of liraglutide compared with dulaglutide in patients with type 2 diabetes mellitus

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Background
Was performed an open study in 2 parallel groups to compare the efficacy and safety of dulaglutide and liraglutide in combination with Metformin in patients with type 2 diabetes mellitus.
Methods
Thirty-two patients (13 men and 19 women) with type 2 diabetes mellitus with unsatisfactory glycemic control on Metformin monotherapy were examined. The median age was 52 [44; 61] years old, the duration of diabetes was 4.6 [2,5; 9,0] years, median of glycated hemoglobin initially was 8.3 [7,7; 8,6] %; 14 patients were treated with dulaglutide 1.5 mg once a week, 18 patients – with liraglutide 1.2 mg every day.
Results
The duration of the observation was 26 weeks, after this period at the therapy with dulaglutide 1.5 mg/week the glycated hemoglobin descension was -1.09 [0.82, 1.21] %, which was comparable to the results in the group of patients on liraglutide 1.2 mg /day – 1.12 [0.90; 1.25] % ($P=0.78$). Weight loss was more significant on liraglutide – 5.2 [3.5; 6.0] kg. vs. 4.3 [2.5; 5.3] kg. on dulaglutide ($P\leq0.05$). Side effects included nausea (35.7% for dulaglutide and 33.3% for liraglutide ($P=0.9$)), dyspepsia (7.1% for dulaglutide and 11.1% for liraglutide ($P=0.81$)), diarrhea (14.3% for dulaglutide and 11.1% for liraglutide ($P=0.85$)) and decreased appetite (28.6% for dulaglutide and 33.3% for liraglutide ($P=0.9$)). The amount of hypoglycemia was comparable in both groups and no severe hypoglycaemia was reported.

Conclusions
According to the results obtained, dulaglutide and liraglutide were comparable in effectiveness with respect to the reduction of glycated hemoglobin, while the number of side effects was comparable, but the decrease in weight on liraglutide was significantly higher than on dulaglutide.

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P477

A localized painfull rash induced by linagliptin in a patient with type 2 diabetes

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Introduction
Although dipeptidyl peptidase-4 (DPP-4) inhibitores are generally safe and are associated with less side effects compared to other oral antidiabetic medications, they could also be associated with some side effects including skin rash. Herein we report the first case of a type 2 diabetes patient who developed a painfull maculopapular rash induced by linagliptin, a widely used DPP-4 inhibitor.
Case presentation
A-54-year old female patient with newly diognesed Tip 2 diabetes admitted to our outpatient clinic due to nausea, vomiting, polyuria and polydipsia. Physical examination was normal except for a reduced skin turgor and tonus. On biochemical analysis, her fasting plasma glucose (FPG), HbA1c, white blood cell count (WBC), serum creatinin, BUN and C-reactive protein levels were 300 mg/dL, %9.8, 17.000 (%70 neutrophil), 1.7 mg/dL, 60 mg/dL and 3 mg/L (<5 mg/L), respectively. She didn't have ketonuria or acidosis and the serum potassium level was normal. One day after starting rehydration with isotonic saline infusion and intensive insulin therapy for acute renal injury and hyperglycemia, the skin turgor and tonus, FPG, serum creatinin, BUN and white blood cells count returned to normal. On the 3th day after admission, treatment with metformin was started, however, she developed dyspeptic complaints and watery diarrhea. Therefore,metformin was stopped and treatment with linagliptin was started. However, one day later, the patient developed a painfull, maculopapular rash without itching, on the palmar sides of the both hands. The linagliptin treatment was stopped. A skin biopsy revealed an eosinophilic superficial dermatitis. So, a diagnosis of an allergic skin reaction due to linagliptin was made.Treatment with bethametasone ointment was started. Four days after cesation of linagliptin and starting treatment with bethametasone oinment, the pain and maculopapular rash were completely dissapeared.
Conclusion
The present case suggests that like other DPP-4 inhibitores such as sitagliptin and vildagliptin, linagliptin may also cause skin reactions. Therefore, attention should be paid to patient receiving this class of drugs and treament should be stopped after appearance of skin reactions. However, it is not well known whether cross reaction would develop after switching to another DPP-4 inhibitor in patients with skin rash developed after starting a DPP-4 inhibitore. However, close follow-up of patients with skin reactions after a DPP-4 inhibitor is necessary to prevent serious skin reactions.

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P478

Preservation of residual β-insulin function in a patient with a type 1 diabetes treated early by fingolimod for multiple sclerosis

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Introduction
Type 1 diabetes (T1D) and multiple sclerosis (MS) are autoimmune diseases with common immunological mechanisms. Type 1 diabetics have an increased risk of MS. The aim of this work is to report a clinical observation of a partial preservation of β-cell function in a type 1 diabetic patient treated early by Fingolimod for MS.
Observation
A polyuro-polydipsic syndrome and a weight loss of 10 kg led to the diagnosis of T1D (typing HLA DR4/DR3, Anti-GAD and anti-IA2 antibodies positive: 3.7 and 3.2 IU/ml respectively, C-fasting peptide: 0.41 ng/ml and HbA1c: 14%) in a 15-year-old patient treated by a basal-bolus insulin. 4 weeks later, the majoration of old balance disorders and the onset of an epileptic seizure (without hypoglycemia), revealed a relapsing-remitting MS, justifying the introduction of an immuno-modulatory treatment by Fingolimod (a sphingosine 1-phosphate receptor modulator which causes a redistribution of T lymphocytes to lymphoid organs, reducing the circulation of auto-aggressive lymphocytes) 11 weeks after discovery of T1D. After 31 months under Fingolimod, glycemic balance is perfect (HbA1c between 5.8 and 7%) with partially preserved insulin reserves (fasting C-peptide around 0.50 ng/ml). According to results of studies on mouse models, Fingolimod preserves β-cell function by modulating the immune response and inhibiting apoptosis (Hosik M Diabetes Metab Res Rev 2013). At 33 months post-diagnosis of T1D, insulin boluses were replaced by Repaglinide at mealtime (before change: fasting C-peptide at 0.5 ng/ml and postprandial at 1.5 ng/ml, glycemia respectively at 1.93 g/l and 2.67 g/l. 4 months after change: fasting C-peptide at 0.51 ng/ml and postprandial at 1.85 ng/ml, glycemia respectively at 1.11 g/l and 1.66 g/l). Metformin has been introduced to reduce insulin resistance in a context of overweight, combined with a GLP-1 analogue. The glycemic balance remains correct with HbA1c between 7 and 8.1% without glycemic fluctuations. The insulin reserves remained stable (12 months after change the fasting C-peptide remains around 0.50 ng/ml).
Discussion
Although slow-type 1 diabetes or a protective effect of the GLP 1 analogue can not be excluded, the early introduction of Fingolimod probably helped to preserve the residual β-cell function, which is consistent with results of work on murine models. This opens new therapeutic hope for management or prevention of T1D as well as the use of Fingolimod in diabetes cell therapy (Bowers J Biomed Mater Res 2017).

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Treating depression in insulin dependant diabetics improves glucoregulation

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Bacground
It is disputable whether negative effects of comorbid depression in patients with type 2 diabetes can be diminished by treatment of depression. The primary aim of this study was to assess whether addition of antidepressants to existing insulin therapy would further improve glycemic control in these patients. A secondary objective was to assess whether such treatment impairs their lipid and inflammatory status.
Material/methods
Total of 50 patients with poorly controlled diabetes (defined as HbA1c $>8\%$) and BDI-II >14 and psychiatric confirmation of depression, in the abscence of any uncontrolled medical condition, entered the 6 month interventional phase with SSRI class antidepressants.
Results
During the interventional phase HbA1c dropped from $8.5\% \pm 1.2\%$ to $7.7\% \pm 0.7\%$ ($P<0.001$). BDI-II scores improved significantly from 30.4 ± 13.2 to 23.5 ± 11.0 ($P=0.02$) during the interventional phase. A positive linear correlation between improvement in depression scale and improvement in glycemic control was observed ($R^2=0.139$, $P=0.008$). Lipid profile and inflammatory status did not change significantly during interventional phase.
Conclusion
Patients with poorly controlled diabetes and comorbid depression might benefit from screening and treatment of depression with SSRI antidepressants by achieving an incremental effect on glycoregulation. This therapy did not have any adverse effects on lipid profile or inflammatory status.

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Comparative analisis of multiple daily injection of insulin and continuous subcutaneous insulin infusion regimes in children and adolescents with type 1 DM in Uzbekistan

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Background
Insulin pumps, devices for continuous subcutaneous insulin infusion have become fundamentally new and progressive step in the treatment of diabetes. To date, there has been no experience with the use of insulin pumps in Uzbekistan
Aims and objectives
To evaluate the effectiveness of insulin pump therapy in comparison with the regime of multiple daily injections (MDI) of insulin.
Materials and methods
Forty children and adolescents with type 1 diabetes from 5 to 17 years (28 girls and 12 boys) were examined. All patients were divided into 2 groups. Group 1 consisted of patients who were transferred from the baseline bolus scheme of insulin therapy with human insulin to MDI with combination of a human insulin analog and a short-acting insulin. Group 2 includes patients who were transferred to pump insulin therapy and received ultrashort acting insulins. Glycemia and glycated hemoglobin were monitored Within 12 months,
Results
The comparative analysis showed a significant decrease in glycated hemoglobin ($7.9+0.3$) by 2.3% in group 2, compared with children and adolescents on the MDI regime (HbA1c $7.8+0.3$%, decrease by 1.5%). The proportion of patients with a HbA1c level of less than 7.5% on MDI increased from 20% to 50%, and in the group receiving insulin pump therapy increased from 15% to 50%. Target values of HbA1c <7.5% reached 50% of patients in groups 1 and 2.
Conclusion
On insulin pump therapy HbA1c decreased by 2.3%. The target values of HbA1c reached 50% of the patients in both groups.

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P481

Perinatal outcomes in Mexican women with mild gestational diabetes mellitus without treatment diagnosed by the international association of diabetes and pregnancy study groups criteria

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Aims
To compare the risk of adverse perinatal outcomes (APO) between pregnant women with mild gestational diabetes mellitus (GDM) by International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria without treatment versus women without GDM.
Methods
A retrospective cohort study. We included pregnant women with prenatal care and delivery at our Institution. Group 1, women with mild GDM defined by one abnormal glucose value according to IADPSG criteria; fasting: 5.1–5.2 mmol/l (92–94 mg/dl) or 2 h 8.5–8.56 mmol/l (153–154 mg/dl), which did not receive treatment for GDM. Group 2, women without GDM matched by maternal age and pre-gestational body mass index (BMI). We excluded women with pregestacional diabetes, any chronic disease, and multiple pregnancies.
Results
282 women were included in each group. There were not significant differences in basal characteristics between groups. The newborn weight was significantly higher in group 1 (3042.4 ± 499 g) vs group 2 (2910 ± 565 g) $P=0.003$, however the incidence of neonates large for gestational age (LGA) and macrosomic were similar in both groups 6 vs 5.7% and 2.1 vs 2.2% respectively. There were no differences in the risk of APO such as; preeclampsia, gestational hypertension, cesarean, preterm delivery and premature rupture of membranes. In a sub-analysis we showed that LGA was significantly higher in women with pre-gestational BMI ≥ 30 kg/m^2 in both groups.
Conclusions
The risk of APO is similar in Mexican women with mild GDM diagnosed by IADPSG criteria without treatment compared to pregnant women without GDM. The pre-gestational BMI is an independent risk factor for neonates LGA.

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P482

Meta-analysis of clinical efficacy of traditional chinese medicine formula (Simiao Yong'an Decoction) in treatment of diabetic foot meta-analysis of clinical efficacy of traditional chinese medicine formula (Simiao Yong'an Decoction) in treatment of diabetic foot

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Objective
To evaluate the efficacy and safety of Traditional Chinese medicine formula (Simiao Yong'an Decoction) in the treatment of Diabetic foot (DF).
Methods
A comprehensive retrieval was made in PubMed, EMRS, EMbase, The Cochrane Library, CNKI, WanFang and other databases to collect randomized controlled trials (RCTs) on the treatment of DF with Simiao Yong'an Decoction (from the establishment of databases to Dec 2017). Two reviewers independently screened literature, extracted data and assessed the risk of bias. RevMan 5.3 software was used to perform Meta-analysis. The control groups was treated by conventional Western therapy (anti-infectives, anticoagulant, promote the blood circulation), while the intervention groups was treated by Simiao Yong'an Decoction. There was no statistically significant on the levels of blood glucose between these two groups. The curative effect was measured by clinical curative effect, the blood flow in the dorsalis pedis, ankle brachial index, side effects. The therapy was sustained at 8 weeks.
Results
Seven RCTs were enrolled in the study, with a total of 485 patients. The Meta-analysis results showed that compared with the conventional therapy, Simiao Yong'an Decoction had advantages in improving clinical curative effect (OR = 1.15, 95% CI = [1.07, 1.24], $P=0.000\ 2$), and enhance the blood flow in the dorsalis pedis (WMD = 1.40, 95% CI = [0.94, 1.86], $P<0.000\ 01$) and increase the ankle brachial index (WMD = 0.07, 95% CI = [0.02, 0.12], $P=0.005$). While there was no statistically significant on adverse events.
Conclusion
Simiao Yong'an Decoction may have advantages over Western medicine in the treatment of DF, and it is a form of recommendable adjuvant therapy for DF. In view of the limited quantity and quality of the included studies, it is needed to verify with more high quality randomized controlled trials.

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P483

Maculopapular rash developed after initiation of U-300 glargine insulin in a patient with type 1 diabetes mellitus

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Introduction
U-300 insulin glargine has been used as a concentrated form of glargine. Skin and subcutaneous tissue disorders (eg, rash, pruritus, and urticaria) have been reported with insulin glargine. But to our knowledge, maculopapular rash has not been reported with use of U-300 insulin glargine. We present a patient with type 1 diabetes mellitus(DM) developing maculopapular rash after initiation of U-300 glargine insulin.
Case Report
37 year-old female patient followed up with type 1 DM for 8 years was referred to our clinics with the signs of hypoglycemia including intermittent palpitation, sweating and tremor. She had neuropathic complaints as "stocking glove" paresthesia. She had been taking multiple daily insulin injection (3*10 unit regular, 1*12 unit U-100 glargine insulin). On physical examination; vital signs were stable and systemic examination was unremarkable. Serum biochemistry and hormonal analysis revealed as fasting blood glucose(FBG) (159 mg/dL), postprandial blood glucose(PPBG) (231 mg/dL), HbA1c (6.6%), C-peptide (<0.10 ng/mL), creatinine (0.65 mg/dL), ALT (12U/L), Na (136 mmol/L), K (4.27 mmol/L), TSH (1.28 IU/mL) and free T4 (0.79 ng/mL). Due to frequent hypoglycemic attacks, the patient was accepted as "Brittle diabetes". Insulin dosage was titrated according to monitorization of blood glucose. However, due to persistent increased morning fasting glucose levels, U-100 insulin glargine was increased to a dose of 22 unit. Nocturnal hypoglycemia occured after this adjustment; therefore, U-300 insulin glargine was initiated instead of U-100 insulin glargine. The frequency of nocturnal and daytime hypoglycemia, and glycemic variability decreased, and glycemic regulation was maintained with

U-300 insulin glargine of 9 units. 3 weeks later, we detected maculopapular rash on her anterior chest, left arm and deltoid (Photograph-1). Then, U-300 insulin glargine was cessated, and rash was regressed.
Conclusion
We report a case with maculopapular rash developed in a diabetic patient after initiation of U-300 insulin glargine for a first time. Timely cessation of U-300 insulin glargine was resulted in resolution of the rash. Our case highlights rare and lesser known side effect of U-300 insulin glargine.

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P484

Dapagliflozin after liraglutide in patients with type 2 diabetes

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Objective
To evaluate the efficacy of dapagliflozin for glycemic control and progression of weight loss after stabilization with liraglutide 1.8 mg.
Patients and methods
Descriptive study: patients with tipo 2 diabetes (DM-2) in treatment with metformin and liraglutide 1.8 mg, optimal metabolic control, which after stabilization in weight loss, liraglutide is suspended and dapagliflozin is added. Variables analyzed baseline and at 6 months after treatment change: age, sex, time of diabetes evolution, Body mass index (BMI), abdominal perimeter (BP), systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL, HDL, triglycerides (TG), uric acid (UA). Statistical analysis: comparing means with Student's test.
Results
15 patients with DM-2 treated with metformin 1000 mg/12 h and liraglutide 1.8 mg with optimal glycemic control and stabilized weight loss. 60% women Age: 56±7.5 years. Time of diabetes evolution: 8±4.1 years. Weight loss achieved 6 months after the change of treatment was 9.7±11 Kg. No side effects were recorded. The treatment change was satisfactory for all patients.

	Basal (mean ± SD)	6 months (mean ± SD)	P
Weight (Kg)	96.3±11	89.5±11	0.1
BMI (kg/m^2)	34±2.7	31.5±2.8	0.02
BP (cm)	109.5±9.5	105.3±9	0.2
SBP (mmHg)	137.6±10.5	130.3±9	0.05
DBP (mmHg)	86.6±14.5	72.8±8.1	0.003
HbA1c (%)	7±0.2	6.5±0.3	0.001
LDL (mg/dl)	95±115.7	80.5±11.6	0.01
HDL (mg/dl)	45.3±7.4	48.6±4.8	0.2
TG (mg/dl)	178.6±69.8	124.6±37.3	0.01
UA (mg/dl)	7.1±0.8	6.3±1.1	0.002

Conclusions
The change of treatment of liraglutide 1.8 mg to dapagliflozin in patients with optimal glycemic control and stabilization weight loss, achieves a progression in weight loss and improves the metabolic control of the patient with DM-2. The change of treatment was satisfactory for all patients.
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P485

Canagliflozin after liraglutide in patients with type 2 diabetes

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Objective
To evaluate the efficacy of canagliflozin 100 mg for glycemic control and progression of weight loss after stabilization with liraglutide 1.8 mg.
Patients and methods
Descriptive study: patients with type 2 diabetes (DM-2) in treatment with metformin and liraglutide 1.8 mg, optimal metabolic control, which after stabilization in weight loss, liraglutide is suspended and canagliflozin 100 mg is added. Variables analyzed baseline and at 6 months after treatment change: age, sex, time of diabetes evolution, Body mass index (BMI), abdominal perimeter (BP), systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL, HDL, triglycerides (TG), uric acid (UA). Statistical analysis: comparing means with Student's test.
Results
Eighteen patients. 50% women Age: 55.61±7.1 years. Time of diabetes evolution: 7.7±5 years. Weight loss achieved 6 months after the change of treatment was 6±2.5 Kg. No side effects were recorded. The treatment change was satisfactory for all patients.

	Basal (mean ± SD)	6 months (mean ± SD)	P
Weight (Kg)	97.5±10.8	91±10.9	0.1
BMI (kg/m^2)	35.2±2.3	33.1±2.2	0.01
BP (cm)	110.3±9.4	105.7±8.6	0.1
SBP (mmHg)	137.5±8.5	128.9±7.1	0.002
DBP (mmHg)	84.6±14.4	75.5±7.1	0.02
HbA1c (%)	7±0.2	6.5±0.3	0.000
LDL (mg/dl)	104.5±32.1	89.3±22	0.11
HDL (mg/dl)	46.8±8	49.5±6.7	0.3
TG (mg/dl)	164.5±74.2	125.8±44.4	0.06
UA (mg/dl)	7.2±0.9	6.5±1.2	0.05

Conclusions
The change of treatment of liraglutide 1.8 mg to canagliflozin 100 mg in patients with optimal glycemic control and stabilization weight loss, achieves a progression in weight loss and improves the metabolic control of the patient with DM-2. The change of treatment was satisfactory for all patients. No side effects were recorded.

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P486

Inhibitors SGLT2 after liraglutide in patients with type 2 diabetes

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Objetive
The change of treatment of liraglutide 1.8 mg to dapagliflozin or canaglifonzin 100 mg in patients with optimal glycemic control and stabilization weight loss, achieves progression in weight loss and improves the metabolic control of the patient with tipo 2 diabetes (DM-2). Our objective is to evaluate if there are differences in metabolic control and progression of weight loss in patients treated with canagliflozin 100 mg or dapagliflozin.
Patients and methods
Retrospective descriptive study: patients with DM-2 treated with metformin and liraglutide 1.8 mg, optimal metabolic control which after weight stabilization, liraglutide is suspended and treatment with canagliflozin 100 mg (group 1) or dapagliflozin (group 2) is initiated. Variables analyzed baseline and at 6 months after treatment change: age, sex, time of diabetes evolution, Body mass index (BMI), abdominal perimeter (BP), systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile and uric acid (UA). Statistical analysis: comparing proportions with the chi-squared and comparing means with Student's test.
Results
Thirty-three patients (group 1: 18; group 2: 15). Baseline characteristics were similar in both groups. Results at 6 months of treatment change:

	Group 1 (mean ± SD)	Group 2 (mean ± SD)	P
Weight (Kg)	9.1±10.9	89.5±11	0.7
BMI (kg/m2)	33.1±2.2	31.5±2.8	0.08
BP (cm)	105.7±8.6	105.3±9	0.9
SBP (mmHg)	128.9±7.1	130.3±9	0.6
DBP (mmHg)	75.5±7.1	72.8±8.1	0.3
HbA1c (%)	6.5±0.3	6.5±0.3	1
LDL (mg/dl)	89.3±22	80.5±11.6	0.2
HDL (mg/dl)	49.5±6.7	48.6±4.8	0.9
TG (mg/dl)	125.8±44.4	124.6±37.3	0.06
UA (mg/dl)	6.5±1.2	6.3±1.1	0.6

Conclusions
We did not find differences in metabolic control and progression of weight loss in patients treated with canagliflozin 100 mg or dapagliflozin after stabilization with liraglutide 1.8 mg.

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P487

Second setp in type 2 diabetes, what to choose?

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Introduction
In type 2 diabetes the choice of the second drug after metformina is marked by the basic characteristics of the patient.
Objetive
To analyze in real clinical practice the effectiveness of different antidiabetics.
Material and methods
Observational study including patients with type 2 diabetes, in which we added to metformina different antidiabetics. We revised them 3-6 months from change.
Results
Seventy-three patients were included, 40 were added SGLT2, 21 DDP4, 12 GLP1 agonist. There were not found different between groups in basal or 3-6 month characteristics except on BMI. 3-6 month after the change (table1), triglycerides, glucose, HbA1c and TAS were significantly lower on SGLT-2 group. On IDPP-4, only HbA1c levels were significantly lower than basal. On GLP-1, HbA1c and TAD were significantly lower.

		BASAL	FINAL	P-value
Age	SGLT2		45.17	
	IDPP4		51.54	
	GLP1		47.59	
	p-value		0.273	
Sex (♀-♂)	SGLT2		16–24	
	IDPP4		14–7	
	GLP1		5–7	
	p-value		0.126	
BMI	SGLT2	32.80	31.48	0.098
	IDPP4	26.74	25.31	0.246
	GLP1	38.11	35.10	0.216
	p-value	0.000	0.020	
Total colesterol	SGLT2	187.84	170.14	0.869
	IDPP4	184.36	163.60	0.737
	GLP1	209.00	164.40	0.185
	p-value	0.625	0.950	
HDL	SGLT2	37.31	42.35	0.296
	IDPP4	40.54	40.37	0.265
	GLP1	35.12	39.55	0.522
	p-value	0.690	0.866	
LDL	SGLT2	115.25	102.78	0.081
	IDPP4	106.17	84.62	0.556
	GLP1	132.83	101.11	0.093
	p-value	0.386	0.531	
Triglycerides	SGLT2	252.61	171.62	0.019
	IDPP4	385.00	148.12	0.237
	GLP1	290.37	170.90	0.098
	p-value	0.553	0.799	
Glucose	SGLT2	240.45	136.50	0.003
	IDPP4	203.83	136.00	0.418
	GLP1	228.63	140.00	0.470
	p-value	0.591	0.768	
HbA1c	SGLT2	9.65	7.16	0.000
	IDPP4	9.98	6.87	0.023
	GLP1	10.31	7.32	0.000
	p-value	0.736	0.710	
TAS	SGLT2	133.46	127.86	0.001
	IDPP4	138.67	122.20	0.065
	GLP1	137.70	130.88	0.565
	p-value	0.602	0.579	
TAD	SGLT2	78.94	75.05	0.302
	IDPP4	77.07	73.00	0.753
	GLP1	81.1	73.00	0.027
	p-value	0.708	0.756	

Conclusion
In our series, SGLT2 improve not only glucose and HbA1c, but also systolic blood pressure and triglycerides. DPP4 improve HbA1c and GLP1 improve HbA1c and diastolic blood pressure.

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P488

Short term adherence with discharge recommendation for insulin treatment among patients with type 2 diabetes

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Background
Basal-Bolus (BB) insulin treatment is increasingly used in uncontrolled diabetes patients during hospitalization and is commonly recommended on their discharge. However, the extent of adherence with this recommendation is unknown.
Aim
To determine the short term adherence of type 2 diabetes mellitus (T2DM) patients discharged from internal medicine wards with recommendation for BB insulin treatment.
Methods
Prescription (primary-physician adherence) and purchase (patient-adherence) of long acting and short acting insulins during the 1st month following discharge from internal medicine wards was determined in 336 T2DM patients. Adherence was defined as "full" if prescription/purchase of both basal (long acting) and bolus (short acting) insulin was made and as "partial" if only one kind of insulin was prescribed/purchased. Association between demographic and clinical parameters and adherence was determined.
Results
Primary-physicians' full adherence with discharge instructions was higher than patients' full adherence)76% vs. 62.2% respectively, $P=0.01$). Pre-hospitalization HbA1c was significantly associated with both patient's and physicians' adherence ($9.0\% \pm 2.1\%$ in the full adherence group and $7.7\% \pm 1.3\%$ in the no adherence group, $P<0.01$). Age was negatively associated with adherence of primary-physicians (73 ± 11.2 years in the full adherence group and 65.4 ± 15.5 years in the no adherence group, $P<0.01$). A negative correlation between patients and physicians' adherence and Length of hospitalization was found. When the sole cause of admission was diabetes, close to 100% adherence of both primary-physicians and patients was found.
Conclusion
Short term adherence with discharge recommendation for BB insulin treatment is associated with pre-hospitalization patient characteristics and length of hospitalization

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P489

Dulaglutide; effectiveness in a real world population with type 2 diabetes

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Diabetes is a chronic disease that is often accompanied by multiple comorbidities and health complications such as overweight/obesity. In the late years therapies improving glycemic control while reducing body weight have become a convenient choice to treat diabetes. One of those therapies are GLP 1 receptor agonists. Dulaglutide allows for a once weekly dosing which might improve compliance; moreover its new application device ease the injection. We show the results of HbA1c and weight evolution after starting dulaglutide 1.5 mg weekly in 60 patients (all of them were on metformin and a second drug). Women represented the 42% and the medium age was 59 ± 7 years. We show data after 6 months on dulaglutide. Initial Hba1c was 8.3% (± 1.2). After 6 months it was 7.2% (± 1). Initial weight was 107.7 kg (± 12). After 6 months it was 101.5 kg (± 16). Our results showed an average reduction of HbA1c of 1.1% and average reduction of weight of 6.2 kg. 25% of the patients showed sickness and only a 5% vomits. Only 2 patients had to stop the therapy. There were no other side effects. None of the patients complained about pain or inconvenience related to the injection and all of them found it painless. All the patients rated positively the one weekly dosing. Dulaglutide added to the previous treatment improved glycaemic control in DM2 patients. Dulaglutide added to the previous treatment produced weight loss in DM2 patients. The main side effect was sickness, but it was well tolerated in most of the patients and the therapy was not discontinued. The one weekly dosing and the painless administration was positively rated by all the patients.

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P490

Experience in clinical practice with new long-acting insulins in type 2 diabetes (T2D)

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Introduction
New long-acting insulin analogues (insulin degludec –ID- and insulin glargine 300 U/ml –IG300-) have proved, in clinical trials, that improve metabolic control with lower hypoglycemia rate in T2D.
Objective
To assess characteristics of T2D patients who were given ID and IG300 and to evaluate their effect on metabolic control, weight and insulin dose.
Material and methods
We studied T2D patients whose treatment had been modified. We analyzed weight, HbA1c and insulin dose at baseline and 3-6 months after treatment initiation.
Results
Forty-four patients: 61.4% women, mean age 60,5 ± 10.2 years. T2D evolution time: 15.4 ± 8.6 years. Mean BMI: 31 ± 4.4 kg/m^2. Mean HbA1c: 9.2 ± 1.7%. At baseline, 16% not insulin-treated (4.6% oral antidiabetic drugs –OADs-, 11.4% OADs + GLP1 agonists); 84% treated with long-acting insulin (34.1% insulin glargine, 31.8% insulin detemir, 6.8% pre-mixed insulin, 11.4% insulin NPH) + other therapies (61.4% OADs, 31.8% GLP1 agonists, 25% short-acting insulin). Reason to change: IG300: 91% poor metabolic control, 4.5% twice-daily basal insulin, 4.5% hypoglycemia; ID: 54.5% poor metabolic control, 27.3% twice-daily basal insulin, 18.2% hypoglycemia (*P* 0.025). Baseline: no differences in age, T2D evolution time, BMI or HbA1c. ID group had higher dose of basal insulin –BI- (50.7 ± 31.7 vs 29.4 ± 19.8; p 0.033), total daily dose –TDD- (59 ± 30.3 vs 37.7 ± 44.9, *P* 0.036) and units per kg –U/kg- (0.8 ± 0.4 vs 0.4 ± 0.5; *P* 0.031) vs IG300 group. 3–6 months after: no differences between groups. ID: significant drop in HbA1c (1 ± 1.3%; *P* 0.003), BI dose (7.7 ± 14.5 U; *P* 0.008), TDD (8.9 ± 13.3; *P* 0.016) and U/kg (0.8 ± 0.4 vs 0.6 ± 0.3; *P* 0.02), maintaining weight. IG300: significant drop in HbA1c (0.8 ± 1.7%; 0.037), maintaining BI dose, TDD, U/kg and weight. Patients switching from other insulin to ID required a significantly lower dose of IB and U/kg, unlike to those switching to IG300 (−7.7 ± 14.5 vs 5.5 ± 14.2; *P* 0.003 and 0.13 ± 0.1 vs 1.7 ± 0.2 U/kg; *P* 0.011 respectively).
Conclusions
ID was chosen in patients with high insulin requirements, not only to improve metabolic control, but also to reduce hypoglycemia and insulin dose, while IG300 was mainly used in not insulin-treated patients and in those with poor metabolic control.
A lower dose of insulin is required with ID vs IG300.

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P491

Six months of retrospective glycemic control and anthropometric outcomes in type 2 diabetic patients with new dapagliflozin treatment; actual clinical experience data from single center

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Introduction
SGLT2 inhibitors have been an important step in the treatment of diabetes. With numerous controlled experimental studies of these antidiabetic drugs, evaluation of real-life data after entry into clinical practice is an important condition. In our study, it was aimed to evaluate short-term results on glycemic control and weight loss in a narrow group of patients in the single tertiary medical center.
Methods
The study was retrospectively designed and 20 type 2 diabetic patients who had started dapagliflozin in the last 1 year and who had anthropometric and glycemic control data at 3-6th months were included in the study. Data of the patients who did not undergo non-routine administration and whose other antidiabetic treatments were not changed were collected from medical hospital records.
Results
The mean age of the twenty patients was 54.95 years, 25% male and 75% female, mean duration of diabetes was 10.8 years. The mean HbA1c level before dapagliflozin was 8.42%, while it was 7.57 in third and 7.85 in sixth months. Fasting blood glucose levels were found 186.8, 141.6 and 142.2 mg/dl and postprandial glucose levels were found 262.1, 183.9 and 187.1 mg/dl at the 0-3-6th months respectively. Weights were reduced from 87.8 to 84.1 and 83.4 kg, BMI from 33.3 to 31.3 and 31.5 kg/m^2. There was a corresponding decline (107.7 → 106.2 → 106.1 cm) in the waist circumferences. In patients using insulin (n = 5, 25%) weight reduction was slightly lower (average −5.1 to −2.4 kg) but glycemic control was better (HbA1c in the insulin using; 9.54% → 7.70% → 8.30%, non-using; 8.02% → 7.53% → 7.69%). Improvement in glycemic control was more pronounced when diabetes age < 10 years (n = 9, 45%) compared with those of ≥ 10 years.
Discussion
It has been shown that SGLT2 inhibitors provide glycemic control without increasing the risk of hypoglycemia by causing glycosuria with the effect on the glucose reabsorption in the proximal tubules and dependent on serum glucose level. Studies have shown that they reduce HbA1c levels by between 0.5-1% on average and cause weight loss around 5%. The data on our study were found to be consistent with these findings. In addition, indicate that SGLT2 inhibitors are more effective for glycemic control in patients with diabetes mellitus less than 10 years and using insulin, and better in terms of weight control in the patients who do not use insulin.

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P492

Can patient profile influence on GLP1 analogues prescription among physicians?: patient selection and perspectives

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Introduction
The use of glucagon like peptide 1 analogues (GLP1a) for the treatment of type 2 diabetes mellitus (T2DM) is growing. After a decade-long effort to improve the pharmacokinetics of GLP1, a number of GLP1a are currently available on the market. With a view to identifying patient characteristics that could influence physicians' prescription of different GLP1a we carried out this observational study in routine clinical practice conditions. Outcomes after add-on these drugs were described as well.
Methods/design
The study was based on a retrospective design and the following variables were collected to identify potential influencing factors in patient profile at baseline: gender, age, time of evolution of T2DM, body mass index (BMI), HbA1c level and treatment with insulin. To measure outcomes, changes in HbA1c and BMI at 6 months after add-on, were assessed.
Results
75 poorly controlled patients with T2DM who received any GLP1a as add-on therapy were analysed. There was a homogeneus distribution of patients according to the drugs evaluated (one-third of sample for each one: exenatide-LAR [EL], dulaglutide [D] and liraglutide [L]). At baseline, patients on D were older as compared to other GLP1a (D: 60.8 ± 10.8 vs EL: 51.8 ± 10 vs L: 54.2 ± 10.2 years; P = 0.008). There was a nonsignificant trend to prescribe EL in patients with higher BMI ([Kg/m^2]: EL: 41.8 ± 8.8 vs L: 40.7 ± 7.3 vs D: 37.8 ± 6.9; P = 0.17) and D to patients with higher level of HbA1c ([%]: D: 9.2 ± 1.4 vs EL: 8.7 ± 1.7 vs L: 8.5 ± 1.1; P = 0.23). No significant changes in HbA1c and BMI reductions were detected among drugs at 6 months. The highest HbA1c reductions were reached with D (−1.9 ± 1.5% vs EL: −1.2 ± 1.1% vs L: −1.5 ± 1%; P = 0.13). BMI reductions were also equivalent among groups.
Conclusions
According to the trends of use of GLP1a, we can conclude that there is a nonsignificant perception of a higher HbA1c-lowering effect and better security profile for D and a higher weight-lowering effect for EL among physicians. Nevertheless, HbA1c and BMI reductions are equivalent among different types of GLP1a in our routine clinical practice.

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P493

SGLT-2 inhibitors or GLP-1 receptor agonists as add-on to insulin therapy in patients with type 2 diabetes: comparative analysis

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Introduction
Multiple studies have evaluated the efficacy of SGLT-2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP1ra) in patients with type 2 diabetes mellitus

(T2DM). However, their efficacy in clinical practice is less known in patients receiving insulin and few are the studies that compare use of SGLT2i vs GLP1ra as add-on therapy to insulin. This study aims to assess clinical efficacy of both treatments in a cohort of patients with T2DM on insulin and poor glycemic control under routine clinical practice conditions.
Methods/desing
An observational and retrospective study was carried out including 77 T2DM patients on insulin who were added either SGLT2i or GLP1ra to their treatment because of poor glycemic control. Demographic, anthropometric, clinical and therapeutical variables were recorded and compared between groups at baseline and at 24 weeks after add-on. Continuous variables are presented as mean and standard deviation or as median and interquartile range [Q1-Q3] based on data distribution. Categorical variables are presented as frequencies.
Results
SGLT2i was prescribed in 46 patients and 31 patients received GLP1ra. At baseline, both groups were equivalent respect to age, body mass index, weight, time of T2DM duration, dose and regimen of insulin treatment. Female gender rate was higher in GLP1ra group (74.2% vs 30.4%; $P<0.001$). Differences related to HbA1c-lowering effects and weight loss weren't observed between groups at 24 weeks after add-on: HbA1c (SGLT2i vs GLP1ra): $-1.8\pm0.3\%$ vs $-1.7\pm0.3\%$; $P=0.73$; weight loss (SGLT2i vs GLP1ra): -3 ± 0.7 vs -2.6 ± 0.6 kg; $P=0.67$. Moreover, no differences were observed neither in rate of patients who lowered insulin dose nor insulin units according to insulin regimen (basal or basal-bolus): Basal régimen (SGLT2i vs GLP1ra): rate of patients who required any decrease in insulin dose (54.5% vs 43.7%; $P=0.51$), median dose decrease (7 [4–12.5] vs 20 [8–28] IU; $P=0.22$); basal-bolus or basal-plus (SGLT2i vs GLP1ra): rate of patients who required any decrease in insulin dose (33.3% vs 53.8%; $P=0.51$), dose decrease (15.5 [7.5–29.5] vs 14 [8–24] IU; $P=0.96$).
Conclusions
Both SGLT2i and GLP1ra as add-on therapy to insulin result in equivalent HbA1c-lowering effects, weight loss and insulin dose reductions. We didn't find solid arguments focusing on metabolic control, weight-lowering effects or insuline dose reductions to recommend one or another treatment to optimize outcomes in these patients. Further studies exploring patients preferences and adverse events are needed.

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P494

Clinical predictors of therapeutic response to SGLT-2 inhibitors

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Introduction
Predictors for therapeutical response of SGLT-2 inhibitors (SGLT2i) is scarcely studied. The aim of the study was to retrospectively analyse the clinical parameters that contribute to the therapeutic outcomes of SGLT2i.
Methods/design
We enrolled 75 patients with type 2 diabetes mellitus (T2DM), treated with SGLT2i for longer than three months. The patients were divided into two groups: good responders (if HbA1c-lowering effects were $\geq 0.5\%$) and poor responders (if $<0.5\%$), based on pretreatment and post-treatment differences in HbA1c levels. Good responders were also divided into three groups according to decreases of HbA1c: intermediate responders (0.5–0.9%) high responders (1–1.9%), very high responders ($\geq 2\%$). Patients receiving GLP-1 analogues, with glomerular filtration rate below 60 ml/min/1.73 m^2 or any contraindication for the use of SGLT2i were excluded. We used univariate and multivariate analyses to assess pretreatment parameters between the two groups and to identify predictors for response.
Results
78.7% of the patients were good responders. According to decreases of HbA1c, 21.3% were classified as poor responders, 18.7% as intermediate responders, 28% as high responders and 32% as very high responders. Responders had a higher HbA1c at baseline ($9.2\pm1.3\%$ vs $7.5\pm1\%$; $P<0.001$) but no differences according to age, gender, time of evolution of T2DM, body mass index, weight, weight loss, use of other antidiabetic oral agents or insulin were found as compared to poor responders in an univariate analyses. Very high responders had significant ($P<0.001$) higher HbA1c at baseline ($10.4\pm1.1\%$) as compared to high ($8.5\pm0.7\%$) and intermediate responders ($8.3\pm0.6\%$). Multivariate analyses showed that HbA1c at baseline was the only independent predictor for good response to SGLT2i (OR 5.3; 95%CI: 2.1 – 13.1).
Conclusions
Our study showed that level of HbA1c at baseline, but no other parameter, is linked to the therapeutic effect of SGLT2i on T2DM patients and also, related to the magnitude of the response.

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P495

Improvement control rate of blood glucose/blood pressure/blood lipid in diabetes patients by hospital-community integrated management in Shanghai

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Background
Diabetes prevalence and mortality are increasing rapidly and glycemic goals (hemoglobin A1c $< 7\%$) are often not achieved in patients with type 2 diabetes in China, The low control rate of diabetes has become a global problem. The management of community diabetes is the most effective choice to prevent and control chronic diseases.
Objective
To improve the management of diabetes mellitus in community, we analyze the effect of hospital-community integrated management.
Method
541 cases diabetic patients in a suburb community of shanghai from April 2014 to April 2015 were cared with hospital-community integrated management, Include community blood glucose monitoring and regular diabetes education, hospital experts guide the treatment of community doctors etc, and the clinical and laboratory data before and after management was collected, and the control rate of HbAlc, blood pressure, blood lipids and related factors were analyzed.
Results
After one year management, patients with diabetes compared to baseline HbA (%), FPG, 2hPG, HOMA-IR, SBP, DBP, TG, LDL-C, Waist indexes have significant decline ($P<0.05$). the control rates of HbA, blood pressure, blood lipid were increased from 63.40%, 9.98%, 50.46% respectively to 72.27%, 22.18%, 58.96% ($P<0.05$), and the control rates of single, two, three indexes of HbA, blood pressure, blood lipid were all increased from 62.84%, 2.49%, 3.18% respectively to 69.13%, 12.93%, 33% ($P<0.05$).Multivariate Logistic regression analysis shows lack of exercise and control of diets, lower frequency of monitoring blood glucose in community and high systolic blood pressure and triglyceride levels are risk factors of reduction the target rate of HbA to diabetic patients; Age, persons with a lower educational level and high HbA and triglyceride levels are risk factors of decreasing the target rate of hypertension to diabetic patients; Lack of exercise and regular pharmacologic treatment and lower frequency of monitoring blood glucose in community are risk factors of decreasing the target rate of blood lipids to diabetic patients.
Conclusion
The integrated management of hospital and community can improve the control rate of blood glucose, blood pressure and blood lipid in shanghai community, strengthening the blood glucose monitoring in community is an effective method of chronic diseases management of diabetes mellitus

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P496

Abstract withdrawn.

P497

A case with metformin overdose associated acidosis

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Introduction
Metformin-induced lactic acidosis (MALA) is one of the most important drug toxicities with high morbidity and mortality rates. Nonspecific symptoms such as nausea, vomiting, epigastric pain, hypotension, tachycardia, tachypnea, arrhythmia, renal insufficiency, coma and cardiac arrest can be seen. Here we are presenting a case with acidosis due to metformin overdose.
Case
A 36-year-old female patient with a history of type 2 diabetes for three years, presented with glyclazide, metformin + vildagliptin treatment. The patient had a history of thyroidectomy and depression. She has been using levothyroxine. Her family history includes diabetes mellitus in her mother and sister and her father died due to a malignancy. Approximately 2–2.5 hours ago, she were found while sleeping at home and brought to emergency service and declared that she had took 50 tablets of metformin + vildagliptin 50/1000 mg for suicide. The patient had no complaints other than fatigue. She was awake and conscious, cooperated and oriented. The patient was hydrated. Stomach lavage was done, activated charcoal was given after that. Then she was hospitalized to the intensive care unit for further follow-up. At the intensive care unit her initial vitals were normal. Arterial blood gas (ABG) revealed pH: 7.333, HCO3:20.3 mmol/l, lactate:5.7 mmol/l. The hemogram and biochemical values of the patient were normal. In the follow-up her creatinine level reached to 1.4 mg/dl. ABG revealed pH: 6.995, HCO3:7.3 mmol/l and lactate:18 mmol/l. Bicarbonate therapy was started and hemodialysis has been started. After dialysis her ABG revealed pH: 7.409, HCO3: 18.7 mmol/l and lactate:7 mmol/l. The patient did not need dialysis again. Her creatinine levels decreased to 0.59 mg/dl. Just before her discharge ABG revealed pH: 7.453, HCO3:29.5 mmol/l and lactate:1 mmol/l and the she was discharged with recommendations.
Conclusion
The most serious side effect of metformin is lactic acidosis due to the inhibition of hepatic gluconeogenesis and/or conversion of alanine pyruvic acid to glucose. The major component of treatment for metformin intoxication is sodium bicarbonate infusion and hemodialysis treatment since it has not an antidote for overdose. Despite the recommendation of sodium bicarbonate in the presence of severe metabolic acidosis (pH < 7.1), there are theoretical disadvantages. Hemodialysis can be used successfully in patients presenting with MALA due to the chronic use of metformin or acute overdose. As in our case, emergency hemodialysis can be life-saving in cases of metformin-induced metabolic + lactic acidosis.

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P498

Cognitive status, anxiety and depression in patients with type 2 diabetes mellitus on selective DPP4 inhibitor therapy

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Introduction
Cognitive functions and mood (anxiety and depression) are often impaired in diabetes mellitus (DM). Dipeptidyl peptidase-4 inhibitor (DPP-4) has been shown to exert beneficial effects on insulin sensitivity and glycoregulation in T2DM patients. Introducing DPP-4 therapy leads to maintaining control of glucose levels which could ameliorate or slow down further cognitive and mood disorders impairment.
Aim
To evaluate influence of selective DPP-4 inhibitor therapy on cognitive functions, anxiety and depression in T2DM patients.
Method
This was controlled, prospective randomized study with 40 patients with T2DM patients on metformin therapy (63.3 ± 7.4 yrs) and 34 healthy subjects (63.6 ± 6 yrs) matched for age, gender and education. In all subjects, glycemia and Hba1c levels were measured before and six months after DPP-4 inhibitor therapy was introduced. Neuropsychological testing included MMSE, verbal and visual attention span, Trail Making tests A and B (TMTA, TMTB), Test for verbal divergent thinking–phonemic and category fluency (FF and CF), Hospital anxiety and depression scale.
Results
Glycemic control was statistically significantly improved after 6 months in 2DM group (Hba1c 8.32 ± 1.4 vs 7.35 ± 1.19, $P < 0.001$). Some aspects of executive functions (TMTA, TMTB, visual span) were better after 6 months like (TMTA 52.45 ± 20.98 vs 48.00 ± 18.84, $P = 0.014$, TMTB 96.06 ± 26.08 vs 87.91 ± 29.14, $P = 0.003$, visual span 4.18 ± 0.80 vs 4.64 ± 0.90, $P = 0.009$) as well as level of depression (HADSD 5.23 ± 3.83 vs 4.27 ± 3.03, $P = 0.009$).
Conclusion
Improvement in cognitive functions and depression in T2DM patients after 6 months on DPP-4 inhibitor therapy were confirmed. Further clinical studies with longer follow up period are necessary to elucidate our findings.

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P499

Metabolic effects of liraglutide in type 2 diabetic patients.

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Objectives
Obesity and type 2 diabetes mellitus (DM2) are risk factors for non-alcoholic fatty liver disease (NAFLD). The main objective was to study the incidence of NAFLD using the Hepatic Steatosis Index (HSI) in obese patients with DM2. Secondary objectives were to analyse the effect of liraglutide over HSI, body mass index (BMI) and glycated hemoglobin (HbA1c).
Methods
Retrospective observational study of obese type 2 diabetic patients treated with liraglutide during the period 2009-2015. Diagnosis of NAFLD was based on the HSI formula = 8 × (ALT/AST ratio) + BMI (+2, if female; +2, if diabetic).
Results
Study sample of 53 patients, 55% males and 45% females, with a mean age of 49.6 years. 100% of patients presented a positive HSI, which improved in 73.5% of them after treatment with liraglutide. Mean HSI after treatment was significantly lower compared to the previous value (p = 0.008). Mean BMI and HbA1c after liraglutide implementation were also significantly lower than before treatment ($P = 6.004^{-06}$ and $P = 1.074^{-08}$, respectively). Triglyceride levels decreased in 60% of patients without statistical significance ($P = 0.054$).
Conclusions
After 3 months of treatment with liraglutide, there was an improvement in HSI, BMI and HbA1c, as well as a reduction in triglyceride levels.

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P500

Efficacy of glucose control on a combination of dapagliflozin in people with type 2 diabetes mellitus in Korea

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Objective
Dapagliflozin, sodium-glucose cotransporter-2 (SGLT-2) inhibitor, reduces hyperglycemia and body weight by inhibiting renal glucose reabsorption.

However, only a few studies have shown the glycemic efficacy on a combination of dapagliflozin in type 2 diabetic patients in Korean. We evaluated the efficacy and safety of glucose control on a combination of dapagliflozin in people with type 2 diabetes in Korea.
Methods
This is a retrospective, observational study, data from 61 patients with 12 months of dapagliflozin(10mg once-daily) therapy were analyzed, visited medical center from January 2015 to July 2016. We had divided into three treatment groups: first group was dual combination of dapagliflozin and metformin (Group 1); second group was triple combination of dapagliflozin and metformin with sulfonylurea or dipeptidyl-peptidase IV(DPP-4) inhibitors (Group 2); third group was quadriple combination of dapagliflozin, metformin and sulfonylurea with DPP-4inhibitors (Group 3).
Results
Of 61 type 2 diabetic sub-jects, 32 (52.5%) were men and 29 (47.5%) were women. Mean age and duration of DM were 58.5 ± 9.6 years and 11.4 ± 5.6 years respectively; mean body weight and BMI were 72.6 ± 12.1 kg and 27.3 ± 3.6 kg/m^2 respectively. Mean HbA1c and 2-hour postprandial glucose levels were 7.6 ± 1.0% and 194.2 ± 69.8 mg/dl respectively. After 12 months, Dapagliflozin leads to improvement in HbA1, 2-hour postprandial glucose(PP2) in each group. In total, the reductions in HbA1c and PP2 levels were −0.61 ± 0.82% (P = 0.000) and −35.4 ± 62 mg/dl (P = 0.000) respectively. In group 1, the reduction rates in HbA1c and PP2 levels were 0.39 ± 0.80% (P = 0.093) and −19.2 ± 41.0 mg/dl (P = 0.152) respectively. In group 2, the reduction in HbA1c and PP2 levels were -0.93 ± 1.0% (P = 0.018) and −63.1 ± 90.6 mg/dl (P = 0.034) respectively. In group 3 the reduction in HbA1c and PP2 levels were −0.65 ± 0.71% (P = 0.002) and −37.9 ± 61.4 mg/dl (P = 0.001) respectively. There were no serious adverse event including hypoglycemia in dapagliflozin group.
Conclusions
In patients with type 2 diabetes, a combination of dapagliflozin improved glycemic control and reduced body weight reduction with safety.

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P501

Comparison of occurrence of fasting hyperinsulinemia according to type of insulin analogs

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Background
A variety of insulin analogs have been developed and used for the treatment of diabetes mellitus. We often experience elevated serum insulin levels when insulin analog is used, and thus have difficulty in assessing insulin resistance and secretion using serum insulin results. This study aimed to investigate the differences in serum fasting insulin level and insulin antibodies according to the type of insulin analogs.
Method
We conducted a retrospective study from 2007 to 2017 in Kyung Hee University Hospital at Gangdong on the Type 2 diabetes mellitus patients who were prescribed insulin analogs (insulin aspart, lipro, glulisine, detemir, glargine, and premixed insulin). We analyzed fasting insulin titers, insulin antibodies, and glycemic parameters after insulin treatment.
Results
A total of 2272 insulin users were analyzed (average age: 56.4 ± 14.6 years, male: 54.7%). Serum fasting insulin level was higher in long-acting insulin analogs group than in other insulins group and was significantly higher in detemir group than glargine group (detemir group: 52.3 ± 82.2, glargine group: 18.2 ± 26.2; other insulins group: 13.3 ± 23.5, P < 0.001). The proportion of patients with fasting insulin levels above 100 μIU/ml was also higher in the detemir group than in the other groups (detemir group: 16.7%, glargine group: 1.3%, other insulins group: 0.6%, P = 0.001). In addition, the positive rate of insulin antibodies was higher in detemir group than in the other groups. However, fasting glucose, C-peptide level, and HbA1c were not significantly different between groups.
Conclusions
Among insulin analogs, insulin detemir is more likely to cause fasting hyperinsulinemia than other insulins. In this case, it is necessary to examine the insulin antibodies and to consider its association.

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P502

The impact of different glucose-lowering regimens on cardiovascular disease in type 2 diabetes

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Introduction
American Heart Association considers diabetes mellitus (DM) to be one of seven major controllable risk factors for cardiovascular disease. At least 68% of patients age 65 or older with DM die from some form of heart disease while 16% die as a consequence of stroke. Studies conducted in patients with type 2 DM (T2DM) have not confirmed a significant association between a certain types of glucose-lowering drugs and a presence of cardiovascular events.
Aim
To establish a relationship between different treatment regimens in patients with T2DM and a presence of acute or recent cardiovascular event.
Methodology
A cross sectional population based study included patients with both T2DM and myocardial infarction- acute or in the past 1 year, that have been examined in Clinical center of Montenegro during one day. Demographic data were collected, along with a type of treatment for T2DM and current glycoregulation. Statistical analysis was performed using descriptive statistics and Student t-test.
Results
Out of 42 subjects included in study, 23 were female and 19 were male, mean age 66.78 ± 9.67 years. Insulin therapy solely was present in 10 patients (23.8%), combined therapy in 21 (50%) and oral glucose-lowering agents in 11 (26.2%) of patients. The mean value of glycated hemoglobin (HbA1c) in groups respectively was 9.0%, 8.9% and 6.97%. No statistical significance was found between insulin and combined therapy (P = 0.8691), while there were a significant statistical differences between insulin and oral therapy (P = 0.0020) and combined and oral therapy (P = 0.0021).
Conclusion
Glycated hemoglobin, however, could not be a valid surrogate for assessing either the cardiovascular risks or benefits related to diabetes therapy. We concerned that some glucose-lowering agents may impact greater cardiovascular risk but there is no sufficient evidence to support one drug or any combination of other drugs for the reduction of cardiovascular events.

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P503

Evaluation of the risk of hypoglycemias using a questionnaire in patients with type 2 diabetes

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Introduction
The available questionnaires for the detection of hypoglycemia are designed for patients with type 1 Diabetes (T1DM), and do not take into account some characteristics of patients with type 2 Diabetes (T2DM). For instance most of T2DM patients do not perform capillary blood glucose self-monitoring as part of their daily treatment and hypoglycemia might be underestimated. Nevertheless, hypoglycemia can have a negative impact on T2DM patients, in terms of increasing the risk of dementia and mortality. For this reason, a questionnaire was designed to assess the frequency and severity of hypoglycemia in T2DM.
Methods
A prospective study was performed based on the completion of a questionnaire in patients with T1DM and T2DM between July and December 2016.
Results
310 patients were evaluated (160 with T2DM, 76% of which were under insulin treatment). A total of 53.75% of the patients with T2DM reported at least one episode of hypoglycemia in the last six months (88% treated with insulin), and 20% of the patients had symptoms of nocturnal hypoglycemia. Notably, a 33% of the patients with T2DM reported episodes of asymptomatic hypoglycemia. Regarding the severity, 10.6% of patients with T2DM reported at least one episode of hypoglycemia that required assistance of a third person (vs 17.4% of T1DM) and 3.7% of patients presented an episode that required medical assistance (vs. 3.3% of T1DM). We observed a tendency to underestimation of the hypoglycemic events (both by the patient and the physician) in T2DM patients compared to T1DM: 1/3 of patients with T2DM with nocturnal hypoglycemia did not report it to their endocrinologist and in 1/3 of the cases, the physician did not question about hypoglycemia episodes.
Conclusions
This study shows that a significant percentage of T2DM patients had suffered episodes of hypoglycemia, sometimes severe or nocturnal. A questionnaire aimed at the detection of hypoglycemia in T2DM could be useful, although more studies are necessary for its validation.

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P504

The intensity of metabolic processes due to different variants of polymorphism rs1801282 Pro12Ala of the PPARG gene in patients with diabetes mellitus type 2

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Aim
To investigate the effect of the standard dietary recommendations in diabetes mellitus type 2 to the intensity of metabolic processes due to different variants of polymorphism rs1801282 Pro12Ala of the PPARG gene.
Materials and methods
37 patients (11 men and 26 women) in the age of 38–76 years old (the mean age 56.8 ± 9.55 y.o.), with the verified diagnosis of diabetes mellitus type 2 (the mean duration of illness 5.7 ± 3.59 years) and the mean BMI 34.49 ± 4.37 were involved in the study. All the patients were on a 3-month balanced diet, where the simple carbs were excluded and the complex carbs were limited. For the estimation of the body compositions the bioelectrical impedance analysis (BMI) was used. The analysis of the rs1801282 Pro12Ala polymorphism of the PPARG gene in buccal cells was performed using Testgen kits (Russia) for RT-PCR. The spreading of the genotypes and the alleles with the literature data (503 people without diabetes mellitus and prediabetes; European population, 1000 genomes) were compared. The statistical analysis was performed by Graph Pad InStat, Microsoft Excel 2007.
Results
The distribution of the frequency of alleles and genotypes did not correspond to the Hardy-Weinberg equilibrium ($\chi^2 = 8.61$; $P = 0.003$), apparently because of a low investigated selection of the polymorphism rs1801282 of a PPARG gene. The distribution of genotypes of the PPARG gene polymorphism (CC – 59.5%, CG – 21.6% GG – 18.9%) and alleles (C – 70% G – 30%) in the group of patients with diabetes mellitus significantly differed from the control group (CC – 76.9%, CG – 22.1%, GG – 1%; C – 88%, G – 12%; OR = 3.09, 95% CI 1.82–5.28; $P = 0.0001$). In the group of patients with the mutant allele G the increase of the comparative quantity of body cell mass was noticed ($-0.92 \pm 5.20\%$) in comparison with the group of patients without the mutant allele ($2.72 \pm 6.87\%$; $P = 0.05$), in time of the absence of the BMI significant changes ($P > 0.05$).
Conclusions
Polymorphism rs1801282 of the PPARG gene has an association with the intensity of the metabolic processes. Thereby, a special meaning has to be due to the personification of not only the medical, but the dietary correction of the carbohydrate metabolism.

Keywords: PPARG, polymorphism, diet, diabetes mellitus type 2
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P505

A latent autoimmune diabetes in adults (LADA) case renamed after six years of diabetes diagnosis when complicated with diabetic ketoacidosis induced by dapagliflozin

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Introduction
LADA (Latent autoimmune diabetes in adults) is an adult-onset and more indolent variety of autoimmune type 1 diabetes mellitus. In autoimmune diabetes, younger individuals typically have a rapid rate of beta-cell destruction and usually present with ketoacidosis, while adults often maintain sufficient insulin secretion to prevent ketoacidosis for many years. LADA is usually misdiagnosed initially as type 2 diabetes due to its late onset but LADA patients are antibody positive and often require insulin therapy within years of diagnosis. We presented a resistant diabetic ketoacidosis case requiring hemodialysis for long-lasting acidosis after starting dapagliflozin in a patient with LADA formerly misdiagnosed as type 2 diabetes.
Case report
A 54-year-old over-weight white woman who had been followed for her euthyroid autoimmune thyroiditis and type 2 diabetes mellitus for 3 years was admitted to our endocrinology out-patient clinics. During another 3-year period she was followed by intensive insulin regimen plus metformin but after initiating a strict diet programme, she had experienced postprandial hypoglycemia episodes on 3×6 units glulisine and 1×10 units glargine insulin. Her glulisine insulin was stopped and dapagliflozin was added to metformin and glargine. At the fourth day of her new treatment, she returned to our emergency department in the state of severe diabetic ketoacidosis (DKA) [glucose 414 mg/dl, arterial pH: 6.82, lactate 4.2 mmol/l, HCO_3: 4.9 mmol/l, pCO_2: 19.8 mmHg, at urinalysis ketonuria (3+), glucosuria (1+)]. İntravenous hydration, insulin infusion, potassium replacement were initiated at our intensive care unit. After 72 hour of her treatment, ketoacidosis was still severe and due to the failure of intravenous bicarbonate treatment also in correcting acidosis, hemodialysis was started. After 3 sessions of hemodialysis, acidosis was relieved and this resistant ketoacidosis treatment could be changed to subcutaneous intensive insulin regimen only at the 8th day of ICU. Metformin and dapagliflozin were not given anymore and she was discharged at the 13th day of admission with intensive insulin regimen. Due to this resistant DKA status, pancreatic islet antibodies were assessed and two of them were measured as positive [Anti-GAD: 3,58 U/ml (reference range: 0-1), ICA was positive]. The diagnosis of the patient were re-evaluated as LADA.
Conclusion
LADA should be kept in mind in adults with diabetes and another autoimmune disease. And gliflozins can cause euglycemic diabetic ketoacidosis especially when the insulin treatment regimen was loosened in intensity in these misdiagnosed patients.

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P506

Awareness of patients with diabetes on the disease

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Relevance
Patients with diabetes are not always sufficiently informed about disease, approaches to its treatment, and the need to prevent complications.

Purpose
To evaluate the awareness of patients about diabetes in inpatient and outpatient settings.
Materials and methods
Participation in the study was accepted by patients with 1 and 2 types of diabetes in inpatient and outpatient settings. The questionnaire consisted of alternations, united in the following sections: taking medications; diet; glucose control; physical activity; adherence to appointments. 74 patients were included in the study.
Results and discussion
1) Education in the school of diabetes. 72% of patients with type 1 diabetes underwent training in the school of diabetes earlier, third (28%) indicated that they attend classes for the first time. Among patients with type 2 diabetes only 33.0% attended classes in the school of diabetes.
2) Self-monitoring of glucose. More than 2 times a day, 75.0% of patients with type 1 diabetes had a glycemia, the remaining 35% – once a day, 1–3 times a week, and 2 – only occasionally. 13.8% control the level of glycemia only in the morning.
3) Nutrition. Differences in the approaches to nutrition in patients with type 1 and 2 diabetes are primarily due to age and lifestyle.
4) Physical activity. Less than half (37.0%), patients with type 1 diabetes regularly exercise, and 63.0% of patients noted that they paid little attention to this. Among patients with type 2 diabetes, 55.8% exercise regularly.
5) Wealth. More than half of patients with type 1 diabetes either feel healthy, 44.4%, or are neutral in the answer to this question (37.0%), and 18.5% do not agree that they are healthy.
6) Compliance with treatment recommendations. Most patients with type 1 and type 2 diabetes (79% and 73% respectively) make efforts to control their condition.
7) Complications. In 24% of patients with diabetes, retinopathy is noted, 10% have polyneuropathy, and 3% have nephropathy. Among patients with diabetes, 9% of patients have retinopathy, 22% have polyneuropathy, and 16% have nephropathy.

Conclusions
- 75% of those surveyed with type 1 diabetes are aware of the importance of the most frequent definition of glycemia. Almost one third of patients with type 1 diabetes rarely have glycemia control.
- In type 2 diabetes, 33.3% of patients erroneously measured the level of glycemia only in the morning, which distorts the results about the variants of glucose values during the day.

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P507

Efficacy in metabolic control and weight loss of combined treatment with GLP-1 receptor analogues and SGLT-2 inhibitors

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Introduction
The emergence of a new generation of antidiabetic drugs (GLP-1RA and SGLT-2i) with complementary mechanisms of action offer new alternatives in the treatment of patients with T2D and poor metabolic control.
Objectives
To evaluate the efficacy of the aGLP-1 and iSGLT2 combination on metabolic control, weight, blood pressure and insulin dose in patients with DM2.
Methods
Observational, retrospective study. We studied T2D patients whose habitual treatment had been modified on their last visit, using a combination of GLP-1RA and SGLT2i.
Results
36 patients: 56% women, age 59.1±10.0 years, T2D evolution time 11.3±6.5 years, 64% taking insulin. They presented: 77% hypertension, 71% dyslipidemia, 18% retinopathy, 8% nephropathy and 8% neuropathy. As GLP-1RA, 40% used liraglutide, 34% dulaglutide, 22% exenatide-LAR and 3% lixisenatide. As iSGLT-2, 90% used dapagliflozin, 6% empagliflozin and 3% canagliflozin. After four months of treatment, there was a significant decrease in weight (100.0±26 kg vs 96.9±25.2 kg), BMI (37.2±8 kg/m^2 vs 35.8±7.6 kg/m^2), HbA1c (8.56±1.2% vs 7.6±0.7%), fasting glycemia (168.6±37.9 mg/dl vs 147.7±34.6 mg/dl) and insulin dose (53.7±40.2 IU vs. 47.0±31.4 IU). Also, we found a significative decrease in AST (30±13.8 U/l vs 24.9±1 U/l), consequently decreasing HSI (hepatic steatosis index; 47.3±9.4 vs 45.5±9.3). There were no significant changes in blood pressure, lipid profile or ALT.
Conclusion
1) We observed statistically significant decrease in weight, HbA1c, fasting glycemia and insulin dose. 2) There was significant reduction in AST. 3) Further studies are needed to distinguish which type of patient benefits more from this combination.

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P508

Insulin requirements and obstetric outcomes in pregnant woment with type 1 diabetes under continuous subcutaneous insulin infusion (CSII)

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Objectives
The gestations in patients with type 1 diabetes are associated with an increase in maternal-fetal complications. Adequate glycemic control during pregnancy has been shown to reduce adverse events. Given that, the treatment with insulin pump improves glycemic control and that pregnancy implies constant changes in insulin resistance, our objective is to analyze the changes in insulin requirements in pregnant patients under CSII.
Materials and methods
This is a retrospective study of 20 women (39 gestations) with a mean age of 34.3 years (range: 28–41) and a mean time of diabetes duration of 19 years (range: 8, 31). Seven therapies were started with gestational desire (35%) and the mean time under CSII was 4.9 years (range: 0.5–12). Statistical analysis with SPSS 20.0.
Results
The average pre-conception HbA1c was 6.90% (S.D.:0.623) and during pregnancy 6.70% (S.D.:0.61). Thougout pregnancy the total insulin requirements increase by 87.5%: from 33.51 (S.D.:8.85) to 62.84 (S.D.:21.16) (Sig 0.00). These modifications compared with the pregestational values are summarized in the following table (Table 1): nine patients experienced miscarriaged (23%) none preceded by severe hypoglucemia and 1 perinatal death. Macrosomia was found in six gestations (15.38%).
Conclusions
1. During pregnancy, total insulin requirements increase by 87%.
2. This increase occurs at the expense of both basal insulin and carbohydrate-to-insulin-ratio:
   - The increase of the basal insulin is marked after the 2nd trimester, reaching statistical significance.
   - The increase in carbohydrate-to-insulin-ratio is significant in all mealtimes after 2nd trimester, being more marked at breakfast, where it increased by 134% at the end of pregnancy (from 1.08 to 2.22).

Table 1 Modification of insulin requirements during pregnancy.

			Carbohidrate-to-insulin ratio		
Tiempo	Total Insulin	Basal Insulin (24h)	Breakfast	Lunch	Dinner
Pregestacional	M:33.51 S.D.:8.85	M:18.03 S.D.:6.83	M:1.08 S.D.:0.74	M:1,02; S.D.:0.30	M:0,94 DS:0.31
1st Trimester	M:34.97 S.D.:7.64 (n.s)	M:17.67 S.D.:6.33 (n.s)	M:1,15 S.D.:0,59 (n.s)	M:1,05 S.D.:0,28 (n.s)	M:0,95 S.D.:0,30 (n.s)
2nd Trimester	M:44.36 S.D.:9.95 (*P*:0,05)	M: 20.49; S.D.:7.04 (n.s)	M:1,57; S.D.:0,79 (*P*:0,000)	M:137; S.D.:0,65 (*P*:0,000)	M:1,35; S.D.:0,68 (*P*:0,007)
3rd Trimester	M:62.74; S.D.:20.27 (*P*:0,046)	M:28,31; S.D.:14.60 (*P*:0.002)	M:2,22; S.D.:1,34 (*P*:0,001)	M:1,52; S.D.:0,49 (*P*:0,000)	M:1,43; S.D.:0,56 (*P*:0,000)

M: mean, n.s: No sig.

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P509

Addition of sodium-glucose co-transporter type 2 inhibitors to diabetic patients type 2 in treatment with glucagon-like peptide-1 agonists: clinical results

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Background
The complex involvement of multiple metabolic defects in the pathogenesis of type 2 diabetes mellitus (T2DM) makes difficult the treatment in monotherapy, therefore, the use of different antidiabetic drugs with different and complementary mechanisms of action could result in better glycemic control with favorable metabolic changes.
Objective
To determine the effectiveness and safety of the addition of a sodium-glucose co-transporter type 2 inhibitor (SGLT2 inhibitors) to patients with T2DM in treatment with a glucagon-like peptide analogue type 1 agonist (GLP1 agonist) and poor metabolic control.
Material and methods
Retrospective observational study. We included all T2DM patients in treatment with a GLP1 agonist who were added a SGLT2 inhibitor due to poor metabolic control. Clinical, biochemical and side effects were analyzed at baseline and after a mean treatment period of 6 months. Statistical analysis (SPSS v. 20.0): Wilcoxon test.
Results
We evaluated 62 patients (31M and 31W) with a mean age (mean ± S.D.) of 54.55 ± 9.19 years and an evolution of T2DM of 12.1 ± 6.5 years. 21.5% were on treatment with Dulaglutide + Dapagliflozin, 19.4% Liraglutide + Canagliflozine, 11.3% Liraglutide + Empagliflozine, 16.1% Dulaglutide + Canagliflozine, 8.1% Liraglutide + Dapagliflozin, 6.4% Dulaglutide + Empagliflozine, 6% Exenatide + Dapagliflozin, 4.8% Exenatide + Empagliflozine, 4.8% Exenatide + Canagliflozine and 1.6% Lixisenatide + Dapagliflozin. At baseline, they had a FPG of 188.4 ± 53.6 mg/dl, an HbA1c of 8.85 ± 1.7%, a SBP of 133.7 ± 12.5 mmHg, a DBP of 77.7 ± 7.7 mmHg, a weight of 95.35 ± 24.05 kg, a BMI of 34.47 ± 6.5 kg/m^2 and a dose of basal insulin ($n = 12$) 35.75 ± 18.82 IU/d (0.38 ± 0.21 IU/kg per day). After a mean treatment period of 6.2 ± 3.2 months, there was a significant reduction in FPG (46.04 ± 61.01 mg/dl less ($P = 0.003$)), HbA1c (1.2 ± 1.7% less ($P = 0.002$)), weight (2.49 ± 5.75 kg less ($P = 0.019$)) and BMI (0.67 ± 1.79 less ($P = 0.02$)). There was no significant reduction in basal insulin requirements (4.16 ± 11.76 IU/d (0.04 ± 0.12 IU/Kg/d) ($P = 0.49$)) and blood pressure (SBP (2.95 ± 14.82 mmHg ($P = 0.46$) and DBP (2.27 ± 10.42 mmHg ($P = 0.25$)). There were no cases of treatment withdrawal due to side effects.
Conclusion
The combination of GLP1 agonists and SGLT2 inhibitors may have an additive or synergistic effect with potential favorable results in terms of improved glycemic control and weight reduction.

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P510

Psychopathological determinants of enhanced quality of life in continuous subcutaneous insulin infusion therapy

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Introduction
Scientific progress allowed an evolution on the therapeutic of diabetes mellitus. Continuous subcutaneous insulin infusion therapy (CSII) is one good example, but, beside patients motivation little is known about other psychological factors of success in this therapeutic and how they contribute to quality of life (QoL).
Objectives
Determining some psychopathological predictors of CSII satisfaction and QoL improvement in patients on CSII therapy.
Patients and methods
We gather a sample of 49 diabetic patients in CSII therapy, 59.2% female, with a mean age of 37.9 ± 11.4 years, disease duration of 21.4 ± 8.5 years and a mean CSII usage time of 5.7 ± 2.1 years. We applied the following questionnaires: the insulin delivery system rating questionnaire, the audit of diabetes-dependent quality of life and the brief symptom inventory (BSI). Spearman correlations were used for statistical analysis. A two-tailed value of $P < 0.05$ was considered statistically significant.
Results
First of all we noticed that psychopathological symptomatology was inversely correlated with CSII satisfaction ($r = -0.44$; $P = 0.004$) and overall QoL ($r = -0.43$; $P = 0.003$). The perception that CSII is helpful concerning glicemic variability is the most important contributor to QoL ($r = 0.34$; $P = 0.02$). Results point out that patients who check their blood glucose more often tend to report less worries about diabetes complications, glicemic variability and daily self-security ($r = -0.35$; $P = 0.01$). Nevertheless, 48.9% of patients reported that checking their blood glucose more than four times daily is more than they would like and this fact alone decreases significantly their QoL ($r = -0.47$; $P = 0.001$). Regarding the BSI we noticed that patients with low interpersonal sensitivity tended to report less embarrassment in using CSII therapy ($r = 0.45$; $P = 0.001$). We also found that patients with higher obsessive compulsive symptomatology stated more daily activity interference in CSII therapy, namely, wearing desired clothes ($r = 0.42$; $P = 0.003$), sleep patterns ($r = 0.53$; $P \leq 0.001$), eating habits ($r = 0.30$; $P = 0.04$) and exercising ($r = 0.35$; $P = 0.01$). Lastly, family support, reflected in the form of not arguing attitude, seems to be a psychopathological protector ($r = 0.36$; $P = 0.01$).
Conclusions
In our sample is clear that CSII therapy contributes positively to QoL. However, in order to maximize its impact, it seems relevant to monitor patient's psychopathological register. Addressing these issues previously will probably provide patients and their families with more adaptative strategies in order to enhance better glicemic control.

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P511

Effects of *opuntia ficus-indica* plant extract ingestion on glucose and insulin plasma levels during oral glucose tolerance test

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Background
Cladodes of the nopal *opuntia streptacantha* (prickly-pear cactus) have been traditionally used for the treatment of diabetes in Mexico. Limited data from studies in experimental animals and humans with prediabetes or type 2 diabetes (DM2), have shown promising antihyperglycemic effects using plant extracts of the *streptacantha* and *ficus-indica opuntia* species. The purpose of this study was to assess the effect of *opuntia ficus-indica* plant extract ingestion on plasma glucose and insulin levels in healthy subjects as well as in subjects with prediabetes or diabetes.
Methods
A total of 35 subjects were studied, subdivided in two groups: subjects with normal glucose tolerance (Group A) and subjects with either prediabetes (IGT and/or IFG) or DM2 treated with diet and/or metformin (Group B). All subjects underwent a 75 g oral glucose tolerance test (OGTT) and plasma glucose and insulin levels were measured at 0, 30, 60, 90 and 120 min. Up to 4 weeks later, subjects underwent a 2nd 75g OGTT, during which they ingested 1000 mg of *Opuntia ficus-indica* dry extract (in a capsule form) 30 min prior to glucose ingestion. Glucose and insulin levels between the two OGTTs were compared by longitudinal analysis.
Results
Group A consisted of 13 healthy subjects (31% male, age 41 ± 15 years (mean ± standard deviation), BMI 28 ± 5 kg/m^2, waist circumference 90 ± 15 cm) and Group B of 22 subjects (16 with prediabetes and six with DM2, 55% male, age 54 ± 14 years, BMI 28 ± 4 kg/m^2). In both Groups A and B, co-administration of the plant extract prior to the 75g OGTT did not result in significant changes in the area under the curve for glucose or in the glucose and insulin levels at any time point (P = ns). At the end of the OGTT (120′) in Group A, were 106 ± 26 versus 102 ± 24 mg/dl, and 29 ± 19 versus 26 ± 22 μIU/ml, respectively ($P > 0.05$). In group B, glucose and insulin values were: 159 ± 70 versus 150 ± 65 mg/dl, and 56 ± 61 versus 43 ± 30 μIU/ml, respectively (P = ns).
Conclusion
Short-term administration of *Opuntia ficus-indica* extract in individuals with normal glucose tolerance, prediabetes or diabetes did not affect glucose and insulin levels during OGTT. To further explore a possible antidiabetic effect, larger studies and long-term administration of this plant extract are required.

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P512

Predictive factors of starting insulin in gestational diabetes' Management: About 191 cases

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Introduction
Gestational diabetes' (GDM) intensive management of with adequate insulin therapy prevents maternal, fetal and neonatal complications associated with hyperglycaemia.
Objective
Identify predictive factors for starting insulin in gestational diabetes' management.
Methods
We report a retrospective study conducted from January 2010 to December 2016, involving 191 patients followed in the Endocrinology - Diabetology Department of Ibn Rochd University Hospital of Casablanca for gestational diabetes. The parameters studied were: age, gestational diabetes' recurrence, family history of diabetes, pre-gestational BMI, term of pregnancy at the time of GDM's discovery, initial fasting glucose level and the treatment adopted. Statistical analysis was univariate for all the variables using SPSS version 22.0.0.
Results
Mean age of our patients was 32.5 ± 6.4 years, mean pre-pregnancy BMI 27.7 ± 3.9 kg/m^2. A history of gestational diabetes was found in 14% of pregnant women and macrosomia in 19%. Average term of discovery of the CEO was 23 ± 9.2 SA. Treatment consisted of diet alone in 29% of our patients, insulin therapy in 71%, with a basal regimen in 31% of cases, a basal-plus in 26% and a basal bolus in 43%. Average insulin dose was 0.51 IU/kg/day. Insulin therapy was more frequent when age was greater than 35 years ($P=0.01$), gestational diabetes' discovery term was early (<25 weeks) ($P=0.02$), and initial fasting glucose levels was high (>1.26 g/l) ($P=0.01$). Personal history of macrosomia, gestational diabetes, and overweight were frequently associated with insulin-dependent patients, with no statistically significant relationship.
Discussion
Our results indicates a strong reliance on insulin-therapy in our population, especially since gestational diabetes' term of discovery is early, age is advanced and initial fasting glucose level is high. However, overweight and gestational diabetes history did not have a significant impact.
Conclusion
Insulin initiation predictive factors are important to identify. It is an important step in the management of gestational diabetes to improve maternal and fetal prognosis through close monitoring and rigorous follow-up.

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P513

Safety and efficacy of different insulin regimens in treatment of type 2 diabetic patients who insist to fast during Ramadan 1437 (Hijri) In Fayoum Governorate, Egypt

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Background
Fasting during Ramadan is an obligatory duty for all healthy adult Muslims. However, a lot of type 2 diabetic Muslim patients insist on fasting whatever their condition. There are several potential physiological benefits from fasting, but the prolonged fasting hours during summer provides many questions about safety and efficacy of different insulin regimens for treatment of type 2 diabetic patients during Ramadan. So we aimed in this study is to assess safety and efficacy of different types and different strategies of insulin use in the treatment of type 2 diabetic patients who insist to fast during Ramadan 1437 (Hijri) in Fayoum Governorate.
Patients and methods
This study was conducted on 337 T2DM patients. divided into 3 groups: groups G1 - patients using basal oral regimen, and G2 using premixed insulin regimen and G3 patients on a basal-bolus regimen. For all participants' structured educational sessions, history and clinical examination including blood pressure measurement, waist circumference and BMI, blood glucose, HbA1c, liver, kidney functions and lipid profile before and after Ramadan fast were done. During Ramadan all participants were asked to record readings for the FBS at noon & at 6 pm and a postprandial reading 1–2 hours after breakfast on the following days (2,14,28) and also to record any day that fast was broken with the cause for this.
Results
Hypoglycemic events whether documented or symptomatic were more prevalent (44%&52% respectively) among patients on the basal-bolus regimen with the number of episodes of documented hypoglycemia per patient were higher in this regimen (1.9 ± 0.9) compared to the other two regimens and this difference was statistically significant ($P=0.046$). A statistically highly significant reduction in HbA1c had occurred among patients using premixed insulin $\pm$ oral antidiabetic medications ($P<0.0001$), however, patients on this regimen had the highest prevalence of non-fasting days (44.6%) due to DM.
Conclusion and recommendations
There were comparable results regarding safety and efficacy of the three studied regimens in the treatment of type 2 diabetic during Ramadan. No regimen proved to be superior. Patient education before Ramadan fast is a mandatory step in management.

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P514

Pregnancy and diabetes: an overview about 144 patients

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Introduction
Diabetic pregnancy is a high-risk pregnancy requiring a multidisciplinary approach and close monitoring to prevent maternal-fetal complications. Our study objective was to determine the diabetic pregnancies outcome of in order to improve their management.
Patients and methods
A descriptive retrospective study including 144 patients with diabetic pregnancy followed at the Endocrinology-Diabetology service between January 2016 and September 2017. Data collection was done from medical records. The statistical analysis was done by SPSS. The parameters were studied: age, diabetes type, obstetric history, pre-gestational BMI, weight gain during pregnancy, pre-conceptional HbA1c, for gestational diabetes the term of pregnancy at the time of the discovery and the methods of detection, treatment adopted and the degree of glycemic control, degenerative complications and obstetric complications.
Results
The study included 144 patients with an average age of 31,9ans, 32% had gestational diabetes and 68% pre-gestational diabetes. BMI pre-gestational average was 29.27 kg/m^2 with an average weight gain of 8 kg. Physical activity was performed in 34% of patients. Regarding gestational diabetes, gestational age through discovery was 20 weeks of gestation, discovered during a routine screening in 84.7% of patients and clinical signs in 13% of the cases. For screening methods, fasting glucose was requested by 67.3% against 26% for the 75g OGTT. Regarding the pre-gestational diabetes, 25.7% of patients had type 1 diabetes and 42.3% type 2 diabetes with a mean diabetes duration of 6 years and a mean HbA1c of 8.3%. Retinopathy was present in 22.4% of patients and nephropathy in 4%. For treatment, 80.5% of patients were on insulin and 19.5% in lifestyle and diet. Glycemic control was perfect in 56.3% of patients. Regarding obstetric complications we observed: gestational hypertension in 11.8%, preeclampsia at 4.8%, macrosomia in 8.4%, a preterm labor in 3.5%, malformations in 2%, hydramnios in 2%. The arrested pregnancies were observed in 3.5% of the studied cases.
Discussion
As clearly demonstrated our study, diabetic pregnancy remains a challenge for both the patient and for the health care team given the high number of maternal-fetal complications and the management of difficulty that requires collaboration between diabetologist obstetrician and gynecologist.

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P515

Moroccan woman pregnant diabetic: what dietary errors? About 60 cases

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Introduction
Diet plays an important role in glycemic control in diabetic pregnant women.

Study objectives
To determine the major dietary errors in pregnant women with diabetes.
Patients and methods
A descriptive retrospective study including 60 patients with diabetic pregnancy hospitalized in Endocrinology and Diabetology service between January to December 2016. Data collection was done from medical records.The statistical analysis was done by SPSS. The parameters were studied: age, body mass index (BMI), gestational age, diabetes type, treatment adopted and the degree of glycemic control, pre-conceptional HbA1c, dietary survey: total level of carbohydrates, distribution according to meals, consumption of fast sugars, simple sugars, vegetables, fruit, meat, fish or egg and dairy products a day.
Results
The study included 60 patients with an average age of 30.4 years. Mean gestational age was 22 weeks of gestation, 26.7% had gestational diabetes and 73.3% pre-gestational diabetes. Correct BMI was found in 21.7%patients, overweight at 33.3% and obesity at 45%. 13.3% of patients were on diet and lifestyle rules and 87.7% were on insulin. Glycemic control was achieved in 42.6% of patients. Total carbohydrate intake was excessive (>220 g/day) in 41.7%, while it was insufficient (<180 g/day) in 16.7%. For meal distribution, 53.4% had an excessive intake at breakfast, 56.7% had an inadequate intake of dinner and 51.7% had adequate intake at lunch. Regarding Snacks, 6.7% of patients observed the 3 snacks and 18.3% took bedtime snack. In qualitative terms, major source of carbohydrates came from starchy foods. Furthermore, 28.3% of patients consumed simple sugars with a high glycemic index. Glycemic control was significantly related to the overall carbohydrate intake ($P<0.05$).
Discussion:
Carbohydrate intake recommended for pregnant women with diabetes is between 180–220 g/day divided into 3 meals and 3 snacks. Our study highlights the different dietary errors either in terms of quantity of carbohydrates or their distribution during the day.

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P516

The flexible insulin therapy: satisfaction after the change of treatment? About 73 cases

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Introduction
The Flexible Insulin therapy (FIT) is considered as the therapeutic reference of type 1 Diabetes mellitus. FIT Improves diabetic patientâ€™s quality of life with a great benefit, through food flexibility while providing optimal glycemic control with reduced incidence of both acute and chronic complications. The aim of the study was to evaluate satisfaction on changing treatment as a result of education FIT.
Methods
Prospective study including 73 patients with diabetes type 1 (T1D) who participated on FIT program during the period between April 2013- July 2017. To assess satisfaction treatment after FIT, we used validated questionnaires of satisfaction with the treatment by patient during the consultation after the first week for the Diabetes Treatment Satisfaction Questionnaire Version status (DTQ14s) and at consultation after the third month for the Diabetes Treatment Satisfaction Questionnaire change version (DTQ14c). Patients with an overall score $>$ 25 on the scale of DTQ14s were considered very satisfied, or have assigned a score of 3 in items of DTQ14c.
Results
Mean age of patients was 24.7 years (13-49) with a mean diabetes duration of 7 years (5 months-23 years). The A1C average before the FIT was 9.2% (5 to 13.8%). The evolution after 3 months was marked by improving glycemic control found on lowering HbA1c by an average of 1.5% (0.7–3) a significant reduction in the frequency and severity of hypoglycemia. Regarding the initial satisfaction with the treatment, according to the DTQ14s, patients were generally quite satisfied with their treatment with an average overall score to 21/36 Â$\pm$6.8. After 3 months of the FIT, the DTQ14c showed that 65% of patients were very satisfied with the flexibility of the new regimen, 53% of patients reported a better understanding of their diabetes and 72% were convinced from the convenience of their current treatment. Furthermore, 69% of patients were willing to recommend the FIT to other patients.
Conclusion
Despite the binding nature of carbohydrate counting and blood glucose monitoring, FIT allows positively improvement of patientâ€™s quality of life. Most patients find this quite flexible and satisfactory method, enabling them to better assimilate their illness to better daily management of diabetes.

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P517

Long-term results of continuous subcutaneous insulin infusion on glycemic control and severe hypoglycemias

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Introduction
The use of Continuous Subcutaneous Insulin Infusion (CSII) is expected to improve glycemic control and to reduce hypoglycemia events. However, long-term beneficial results in glucose control are not always observed. We evaluated long-time glucose control and severe hypoglycemias in type 1 diabetic patients using CSII, without continuous glucose monitoring.
Patients and methods
This was a retrospective study of adult type 1 diabetic patients using CSII, assisted at the endocrinology outpatient department of a tertiary hospital. Mean HbA1c was evaluated before CSII, and each year thereafter. Severe hypoglycemias were registered in the year before CSII and the last two years of follow-up.
Results
Ninety patients were studied (66% female). They used CSII since 34 ± 10 years old and had type 1 diabetes since 18 ± 11 years before. Follow-up with CSII was 6.3 ± 2.6 years. HbA1c at baseline and during follow-up with CSII was as follows: Overall, HbA1c significantly decreased ($P<0.001$) in the first year with CSII and remained lower than baseline during the first six years of follow-up ($P<0.05$). However, higher pre-CSII HbA1c was related to a greater decrease in HbA1c until the last year of follow-up ($r=+0.582$, $P<0.001$, $n=56$). In fact, in patients with baseline HbA1c$\geq$8%, this parameter significantly decreased until the sixth year ($P<0.03$), while for patients with baseline HbA1c$<$8%, it decreased only during the first year of follow-up ($P=0.009$). Severe hypoglycemias (78% in patients with baseline HbA1c$<$8%) significantly reduced after CSII ($P<0.05$).

Table 1

	HbA1c % (mean$\pm$sd)						
Patients	Before	First year	Second year	Third year	Fourth year	Fifth year	Sixth year
All	8.1$\pm$1.2	7.4$\pm$1.0	7.6$\pm$0.9	7.7$\pm$1.0	7.9$\pm$1.1	7.9$\pm$0.9	7.8$\pm$1.0
Baseline HbA1c$<$8%	7.2$\pm$0.6	6.9$\pm$0.7	7.1$\pm$0.8	7.1$\pm$0.9	7.2$\pm$0.7	7.5$\pm$0.8	7.3$\pm$0.8
Baseline HbA1c$\geq$8%	8.8$\pm$1.1	8.0$\pm$0.9	8.1$\pm$0.8	8.1$\pm$0.7	8.3$\pm$0.9	8.2$\pm$0.8	8.2$\pm$1.0

Discussion
The best glycemic control was observed during the first year using CSII, eventually in relation to patients' motivation towards the introduction of a new therapeutic approach. Patients with worse baseline glycemic control were the ones who showed larger improvements with CSII. In fact, CSII was effective in long-term glycemic improvement in patients with baseline HBA1c$\geq$8%. On the other hand, CSII also reduced severe hypoglycemic events, which affected mostly patients with baseline HbA1c$<$8%.

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P518

The anxiety and depression disorders in the diabetic type 1 (preliminary results)

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Introduction
The relationship between diabetes and anxiety and depression is bidirectional. Patients with somatic disorders such as diabetes present on average twice more psychiatric disorders than the general population. The aim of our study was to identify the level of anxiety and depression in people with diabetes type 1 and to assess their impact on the clinical features of the disease.

Patients and methods
We conducted a transversal descriptive study including 102 patients with type 1 diabetes, for 8 months (May-December 2017). Assessing anxiety state was made according to the Hamilton and Beck score for depression in Arabic validated. Analysis was performed by SPSS 16.
Results
A mean age was 24 years with, a sex ratio of 1.04 M/F, toxic habits (21.5%), an average diabetes devation of 10.4 years and an uncontrolled diabetes in 83.3% of cases. Degenerative complications were: a retinopathy (20.6%), a nephropathy (20.6%), and neuropathy (16.7%). Incidence of hypoglycemiawas97.05%, irregular follow-up 34.3% of cases. We noted a minor depression (17.6%), a major (11.8%) control glycemia in our patient's depression and a minor anxiety (46%) and major (11%). Anxiety was related to degenerative complications (26.4%). Depression was most noticeable among female patients (20.6%) and contributing factors to this were degenerative complications (14.7%) and lack of financial support (13.72%). Anxiety and depression were not correlated with glycemic control. This highly correlated to the monitoring irregularity.
Conclusion
We emphasize as well the need to integrate research of anxiety and depressive disorders in the care of diabetic type 1 patients, in order and delay the onset of complications.

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Endocrine Disruptors

P519

Intermittent fasting for three months decreases pancreatic islet mass and increases insulin resistance in Wistar rats

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Introduction
It is known that fasting causes several physiological changes in the endocrine pancreas, such as insulin secretion, pancreatic islet metabolism and beta cells redox state. However, there is still no consensus about the effects of intermittent fasting (IF), a fad diet widespread by the media and adopted by individuals seeking rapid weight loss. In the present study, we sought to study the effects of the IF diet for three months in an animal model.
Methods
Thirty-day-old female Wistar rats were submitted to IF for three months. During this time body weight and food intake were recorded. After the treatment the animals were killed, and pancreatic islets, perigonadal white adipose tissue, *extensor digitorum longus muscle* tissue and liver were collected for different analyses.
Results
IF decreased body weight and food intake. The stomach was greatly increased in size. There was an increase in adipose tissue and a decrease in muscle tissue. IF caused elevation of plasmatic insulin levels, both baseline and after glucose administration. *In vitro*, IF pancreatic islets had increased insulin secretion, glucose metabolism and net reactive oxygen species production, while decreased their mass. In addition, impairment in AKT phosphorylation was observed in peripheral tissues indicating insulin resistance.
Discussion
Previous studies showed an increase in orexigenic neurotransmitters production in IF, inducing hunger and hyperphagia in the *ad libitum* feeding days. Our experiments demonstrate that, despite the weight loss, IF treatment induces undesirable effects on tissue homeostasis. Therefore, the hyperinsulinemia registered *in vivo* and *in vitro*, associated with the impairment of glucose tolerance and the decrease in AKT phosphorylation, make clear the occurrence of peripheral insulin resistance. The increased metabolism of pancreatic islets dispersed cells, after IF treatment, indorses the higher insulin secretion. Furthermore, the decrease in the pancreatic islet mass indicates that three months of IF treatment cause severe impairment in glucose homeostasis. In conclusion, intermittent fasting diet may not be healthy to be adopted by individuals seeking rapid weight loss.

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P520

Cognitive impairment and nutritional status in patients admitted to the Department of Internal Medicine

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Introduction
Altered nutritional status is a problem in itself that can complicate a patient's disease. In our hospital, the assessment of nutritional status at hospital admission is protocolized and performed by the Clinical Laboratory automatically, through the CONUT system, for three years ago. Our hospital provides assistance to a population of 120,000 patients, from rural areas and with a high average age. Hospital admissions for cognitive impairment are increasing in our hospital as cognitive impairment is increasingly frequent and these patients often present problems of autonomy that complicate their nutrition and their general care.
Hypothesis
Patients with cognitive impairment who has admitted to the hospital have worse nutritional status than the rest of the patients admitted in Departament of Internal Medicine.
Matearial and methods
Nutritional status was analyzed by the CONUT method; age and sex of all patients admitted to Internal Medicine in our hospital during 2017, compared to those who presented cognitive deterioration as the main diagnosis. Descriptive statistics and contingency tables were applied and X^2 test.
Results
During 2017 there were 1637 hospital admissions in Internal Medicine, 52.8% men and 47.2% women. The average age was 67.57 years. 43.7% did not present risk of malnutrition; 37.9% presented a risk of moderate malnutrition and 18.4% presented a risk of severe malnutrition. In the same period of time, there were 208 admissions due to cognitive impairment, 47.8% men and 52.2% women. The average age of this group was 70.45 years. 32.9% did not present risk of malnutrition; 40.8% presented risk of moderate malnutrition and 26.3% presented risk of severe malnutrition. The general group presented some nutritional disorder in 56.3% of the income compared to 67.1% of the group with cognitive deterioration. The results of nutritional risk comparison between both groups did not show significant differences ($P > 0.001$).
Conclusions
Nutritional status is a condition that must be assessed in all hospital admissions. Cognitive impairments, of different etiologies, can also be severely affected by nutritional status. Although in our series it has not been possible to demonstrate significant differences between the patients of both groups, we believe that malnutrition states play an important role in the evolution of cognitive impairments, so their evaluation should be mandatory. A control of the nutritional status of these patients when they return to their home would be very useful to control the nutritional status of these patients.

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P521

Deleterious effect of low-dose persistent organic pollutants on insulin secretion in pancreatic β-cell

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Low-dose persistent organic pollutants (POPs), especially organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs), have emerged as a new risk factor for type 2 diabetes. We evaluated whether chronic exposure to low-dose POPs affects insulin secretory function of β-cells in humans and *in vitro* cells. Serum concentrations of OCPs and PCBs were measured in 200 adults without diabetes. Mathematical model-based insulin secretion indices were estimated by using a 2-h seven-sample oral glucose tolerance test. Insulin secretion by INS-1E β-cells was measured after 48 h of treatment with three OCPs or one PCB mixture. Static second-phase insulin secretion significantly decreased with increasing serum concentrations of OCPs. Adjusted means were 63.2, 39.3, 44.1, 39.3, 39.7, and 22.3 across six categories of a summary measure of OCPs ($P_{trend} = 0.02$). Dynamic first-phase insulin secretion remarkably decreased with increasing concentrations of OCPs among only insulin-sensitive individuals ($P_{trend} = 0.02$); the insulin levels among individuals with high OCPs were ~30% of those with low OCPs. Compared with OCPs, PCBs showed weaker associations. The decreased insulin secretion by INS-1E β-cells was observed for even 1 pmol/L OCP. The data from human and *in vitro* cell experiments suggest that chronic exposure to low-dose POPs, especially OCPs, can induce pancreatic β-cell dysfunction.

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P522

GLP-1 increases the availability of substrates and prioritizes the use of lipids in muscle metabolism

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The skeletal muscle expresses the Glucagon-like Peptide 1 (GLP-1) receptor, although its effects in this tissue are not well known. Muscles are a major sink of energy substrates. The aim of our study was to examine the mid-term effect of Liraglutide (LIRA), a GLP-1 receptor agonist, in the expression of molecular indicators of the metabolic activity of the muscle, which includes enzymes, transporters, and intracellular signals. Twenty young Spague-Dawley male rats (350-400 g) were treated for seven days with LIRA (100 µg/Kg/12 hours / i.p) or vehicle. Body weight and food intake were monitored daily. After the sacrifice, samples of muscle and serum was stored at −80° C. We studied the expression by rtPCR of mRNA for GLUT-4, CD-36, GAPT-1, GAPT-4, Fosfofructo-kinase-1 (FFK-1), CPT-1, UCP-2, PPAR-gamma and mTOR. In addition, we studied serum proteomics by the profile adipokine Array Kit (RD systems, bio-Techne) for rat. Treatment with LIRA, reduces total food intake (kCal) and body weight gain just in the first 24 hr but not afterwards. LIRA treatment increases the mRNA expression of the translocase CD36 (+74%) that facilitates the entry to the cell of fatty acids, and the expression of the glucose transporter GLUT4 (+317%). LIRA also increases the expression of PPARγ (+800%) involved in the biogenesis of mitochondria and UCP2 (+298%) that promote the oxidation of fatty acids to the detriment of pyruvate from glycolysis. LIRA does not modify the phosphofructokinase 1 nor of CPT-1 expression. In addition, it reduces the expression of glycerol-3-phosphate acyltransferase-1 (GAPT 1, −80%), limiting the formation of mitochondria ketone bodies, and mTOR (−70%), determinant in the synthesis of new fibres. The administration of LIRA also reduce total fat mass (g/100g bw) and the serum circulating levels of total triglycerides. In conclusion, LIRA promotes the entry of fatty acids and glucose in muscle, facilitates the production of energy from fatty acids and the biogenesis of mitochondria, all together improving the efficiency of the muscular energy machinery.

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P523

Plasma levels of perfluoroalkyl substances and risk of type II diabetes mellitus: a prospective nested case-control study

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Background
Perfluoroalkyl Substances (PFAS) have drawn much attention due to environment bioaccumulation potential and their presence worldwide in human blood. Exposure to PFAS is suspected to induce endocrine-disrupting hormonal effects and may be involved in the development of type 2 diabetes (T2D). However, epidemiological evidence is scarce and inconsistent.
Objective
We aimed to investigate the association of PFAS plasma levels on the risk of developing T2D in a Swedish population-based cohort.
Methods
A prospective nested-case control design was applied. Middle-aged subjects participated in a medical examination, completed a lifestyle questionnaire and gave blood samples during 1990-2003. Six different PFAS were measured in plasma. During 10-year average follow-up T2D diagnosis was retrieved from medical records and later validated by specialists according to WHO criteria. A total of 158 T2D cases were matched (1:1) according to gender, age and sample date with participants without T2D (controls). Conditional logistic regressions were used to prospectively estimate the odds ratios (OR) of T2D.
Results
After adjusting for confounders, the risk of diabetes was reduced by 59% in subjects with higher levels of total PFAS in plasma (OR = 0.41; 95% CI 0.18–0.96; *P* trend 0.045; comparing the highest to lowest tertile of the sum of the six standardized PFAS levels). Despite the similar point estimates for the specific individual PFAS (ORs from 0.48 to 0.75), statistical significance was not reached when assessed individually.
Conclusions
We observed that high levels of plasma PFAS in the general population were associated with a lower risk of developing T2D regardless other known risk factors such as age, gender, body mass index and diet. Further work is required to confirm these findings and to clarify potential mechanisms.

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Endocrine Nursing

P524

Evaluation of the technique of insulin injection Analogue in Tunisia in diabetic type 2 and impact on the glycemic balance: study 56 cases

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Introduction
In Tunisia, only about 10% of people with diabetes practice self-injecting insulin analogues. It is 1 Tunisian adult out of 11 who is affected directly by diabetes. Our goal is to assess diabetes patients' knowledge of insulin injection techniques.
Patients and methods
Prospective study of 56 cases of type 2 diabetic patients in the Endocrinology Department CHU Hedi Chaker Sfax Tunisia. All patients had a questionnaire and clinical examination.
Results
Most hospitalized patients (75%) were between 40-66 years old. With male predominance (sex ratio H / F 2). The majority 65% of our diabetic patients had diabetes evolving for more than 14 years. Only 25% of the patients use the analogues regularly and journaled against 65% find insulin injection difficulties similar 25% forgotten, 35% lack of means to buy the special needles of the pens, and others by the refusal the assumption of responsibility by the National Health Insurance Fund (CNAM). The most commonly used insulin therapy regimen is two injections (60%). Patients self-inject insulin analogue in 65% of cases. Only 10% of the cases respect the standards of storage. On the other hand, 75% do not disinfect either the hands or the injection site. The preferred site was the dominant limb arm in 75% of cases. Only 50% introduce the needle without skin fold at 90 ° and inject the insulin dose by pushing on the plunger without forcing. The maintenance of the system in place for 10 s was respected only in 20% of patients. In this work. Only 25% of diabetic patients had a good glycemic control (HbA1 c = 6.8%) who practice similar injections.
Conclusions
A mastery of insulin injection techniques is of paramount importance to achieve a good balance of diabetes; hence the role of the nurse in diabetic and therapeutic education.

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Female Reproduction

P525

Non-alcoholic fatty liver disease and polycystic ovarian syndrome in lean and obese women of reproductive age

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of chronic liver disease in the western world affecting 5-33% of the general population. Polycystic ovarian syndrome (PCOS) is a common endocrinopathy affecting 6-10% of women of reproductive age. In both conditions, insulin resistance (IR) seems to be a common pathogenetic mechanism.

Objective
To investigate the presence of NAFLD in lean and obese women with and without PCOS using biochemistry and imaging modalities such as liver ultrasound (U/S) and computed tomography (CT).
Patients and methods
Eighteen lean and 17 obese control women and 21 lean and 21 obese women with PCOS were studied prospectively. Baseline biochemical profile was followed by a glucose tolerance test and indices of IR were calculated. Ovarian morphology was assessed using transvaginal ultrasonography. Hepatic lipid content was assessed with U/S and CT of the liver.
Results
Mean age was 26 years for all four groups. Mean BMI($\pm$SD) was 21.0$\pm$1.8 kg/m^2 for lean controls and 21.4$\pm$1.9 for lean PCOS and 33.0$\pm$7.4 kg/m^2 for obese controls and 34.6$\pm$6.4 for obese PCOS. Fasting insulin levels and indices of IR showed an incremental continuum trend from the lean controls to lean PCOS to obese controls to obese PCOS. Hepatosteatosis assessed by liver U/S was seen in 15% of lean PCOS, in 37% of obese controls and in 50% of obese PCOS women. Evidence of hepatosteatosis was only found in 1 obese patient with PCOS on liver CT. In the whole population studied there was a negative correlation between waist circumference and mean liver-mean spleen attenuation on liver CT. Age**,** BMI, waist circumference, ALT levels and insulin resistance were independent risk factors associated with NAFLD as assessed on U/S, in lean and obese women of reproductive age with and without PCOS.
Conclusions
NAFLD in more common in obese than lean women with or without PCOS as evaluated by radiologic modalities. Obesity and IR play a determinant role in the development of the disease. Ultrasound is 100% whereas CT is 93% sensitive in detecting NAFLD only when fatty infiltration is at least 33%. Newer methods such as magnetic resonance spectroscopy (MRS) would help to diagnose the disease at earlier stages.

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Neuroendocrinology

P526

Analysis of the results of fasting test in hypoglycemias study

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Methods
Retrospective and descriptive study in a sample of 36 patients with suspected hypoglycemia who were admitted to our Service to perform a 72-hour fasting test. Demographic, clinical data and results of fasting test were analyzed. Endogenous hyperinsulinism criteria were considered to be the combination of plasma glucose $<$55 mg dl, insulin $>$3 mcrU / ml and C peptide $>$ 0.6 ng/ml, in the absence of detection of sulfonylureas.
Results
The average age was 37 years old (81.1% women). The average weight was 66.62 kg and BMI 25.93 kg/m^2. They presented an average evolution of clinical syndrome of 4.6 years. 62.2% reported neuroglycopenic symptoms and 86.5% adrenergic symptoms coinciding with an average capillary blood glucose level of 49.52 mg/dl. 17% referred fasting hypoglycemia and 19.4% postprandial hypoglycemia. The average HbA1C was 5.07%. 91.7% improved their symptoms after supplements with sugar (the rest remitted spontaneously). In the initial evaluation, drug, serious illness and hormonal deficit were ruled out. The test was completed in 26.2$\pm$17.58 hours in 5 patients. Only 3 patients (8.3%) were positive for hypoglycemia due to endogenous hyperinsulinism with an average plasma glucose of 37 mg/dl, insulin 10.05 mcrU/ml and peptide C 3.35 ng/ml, subsequently confirming the diagnosis of insulinoma by imaging tests.
Conclusions
Most of patients completed the fasting test for 72 hours without clinical incidents and without hypoglycemia less than 45 mg/dl, ruling out hyperinsulinemic hypoglycaemia.
In view of these data, it could be concluded that it is important to document the Whipple triad before concluding a possible diagnosis of hypoglycemia to avoid unnecessary tests.

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Nuclear receptors and Signal transduction

P527

Calbindin-d9k interacts with Mucin1, which influences the stability of Hypoxia inducible factor-1a

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Introduction
Hypoxia is involved with various physiological activities from glucose metabolism to tumor suppression. Hypoxia-inducible factor (HIF) is known as master regulator of oxygen homeostasis that triggers more than 1,000 related gene expressions. When hypoxia occurs, HIF1a protein is stabilized and starts transcription. Mucin1 mediates the stabilization of HIF1a in a cytoplasm. In addition, cytoplasmic domain of mucin1 and HIf1a form a transcriptional complex at glycolytic gene promoters. Interestingly, in calbindin-d9k knock out mice, both HIF1a and mucin1 were up-regulated in protein level. Calbindin-d9k has been known as a cytosolic calcium-binding protein. However, our results suggest that calbindin-d9k is involved with the interaction between HIF1a and mucin1. In the result of western blots, immunofluorescent and immunoprecipitation, calbindin-d9k was identified to interact with mucin1, which influence the stabilization of HIF1a.
Materials and methods
Eight weeks old C57BL/6 mice and calbindin-d9K Knockout mice were exposed to hypoxia for 3 weeks. Hypoxic condition was created in polycarbonate chamber with nitrogen supply to remove oxygen. Oxygen concentration were measured and maintained thoroughly about 12$\pm$2% partial pressure of O2. Expression of HIF1a and mucin1 protein in kidney were analyzed by Western blotting. Tissue-specific localization of calbindin-d9k and mucin1 were identified by immunofluorescent in kidney. Co-immunoprecipitation was performed to detect calbindin-d9k and mucin1 protein complex.
Results
In the result of western blot, expression of HIF1a and mucin1 were upregulated in calbindin-d9k knockout mice compared to that of wild type mice exposed in normal atmosphere. However, in hypoxia, both knockout and wild type mice showed similar protein expression. Cabindin-d9k and mucin1 were simultaneously detected at the distal convoluted tubules observed by immunofluorescent. In addition, protein complex between calbindin-d9k and mucin1 was identified by co-immunoprecipitation.
Conclusions
Calbindin-d9k was newly identified to interact with mucin1 protein in kidney. Upregulation of HIF1a protein in calbindin-d9k knock out mice might result from the absence of calbindin and mucin interaction.

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P528

Genotype- Phenotype correlations of TNF-α, IL-6 and Leptin receptor gene polymorphisms in Poly cystic ovarian syndrome

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Introduction
Tumor necrosis factor alpha (TNF-α) and Interleukin-6 (IL-6) are potent immunomodulators and proinflammatory cytokines displaying varied functions. Apart from monocytes/macrophages, they are also produced by the cells in female reproductive tract. Polycystic ovarian syndrome (PCOS) is one of the commonest endocrine disorder amongst women of reproductive age group. Several polymorphisms in the promoter region of the gene TNF-α, IL-6 and Leptin receptors have been described associated with various disease ranging from cancers to PCOS, obesity and infertility. In this context, we evaluated association between PCOS and the promoter single nucleotide polymorphisms of the gene TNF-α –238G/A (rs361525), –308G/A (rs1800629) and –1031T/C (rs1799964); IL-6 –174G/C and *LEPR* 668 A/G.
Material and methods
This is inter-disciplinary study conducted by collaboration between a tertiary care endocrinology hospital, biochemistry department of a teaching medical institute and genetics lab. In this prospective study involving 100 PCOS patients with 100 age matched controls, we employed 3 sets of primers and screened for the known single nucleotide polymorphisms TNF-α, IL-6 and Leptin receptor genes. Apart from qualitative and quantitative evaluation, linkage disequilibrium, multifactor dimensionality reduction analysis and In-silico analysis were performed.

Results
Of identified seventeen haplotypes the haplotype combination "A-A-C-A-C" and "A-G-T-G-C" conferred protection towards PCOS (OR = 0.321, CI = 0.15 – 0.67, $P = 0.002$ and OR = 0.28, CI = 0.11 – 0.73, $P = 0.005$ respectively), while the haplotype combination "A-G-C-A-C" conferred fourfold risk (OR = 3.38, CI = 1.52 – 7.53, $P = 0.0018$) towards PCOS susceptibility. For IL-6 - 174G/C, the percentage of GG, GA and AA genotypes in patients was 24, 44, 32 while it was 25, 45 and 30 in controls respectively. For LEPR gene, the relative risk for the alleles demonstrated a twofold risk of G allele towards disease establishment (OR = 1.62, CI = 1.07 – 2.45, $P = 0.021$).
Conclusions
The present study could not provide a concrete association between the TNF α and IL-6 polymorphisms with PCOS. For Leptin receptor gene, there appears to be role of the AG and GG genotypes, and G allele in contributing towards establishment and progression of PCOS. But further extensive studies are warranted to validate the same phenomenon in the general population and various ethnic groups.
(Key words: PCOS; Rotterdam criteria; Pol;ymorphisms; TNF-alpha; IL-6; Leptin receptor gene; Cytokines; Infertility)

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P529

Association of habitual physical activity with leptin gene expression in visceral and subcutaneous adipose tissues among non-diabetic people

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Introduction
Adipocytokines secreted by adipose tissue are suggested to play a role in the development of obesity-related complications. Leptin is mainly produced and secreted by adipose tissue and appears as an important regulator of energy balance. The relationship between leptin levels and energy expenditure remain unclear. Energy expenditure related to physical activity (PA) is the most variable part of total energy expenditure. There is some evidence that the habitual level of PA may be a significant determinant of leptin concentrations, but the scarce document in leptin gene expression. The aim of this study was to investigate the association between habitual PA and the leptin gene expression among non-diabetic adults.
Materials and methods
Visceral and subcutaneous adipose tissues were gathered from 98 non-diabetic participants aged ≥20, who had undergone elective abdominal surgery. Physical activity was collected using a valid and reliable International Physical Activity Questionnaire (IPAQ)-long form, and the metabolic equivalent of task (MET) was calculated. Respondents were asked to report time spent in PA performed across leisure time, work, domestic activities, and transport at each of 3 intensities: walking, moderate, and vigorous. The mRNA expressions of leptin gene in visceral and subcutaneous adipose tissues were analyzed by Real-Time PCR.
Findings
The mean age of participants (22.7% male) were 41.7 years. No significant difference was observed for leptin gene expression in subcutaneous (−0.135 vs. 0.791, $P = 0.992$) and visceral (−1.582 vs 0.915, $P = 0.891$) fat mass between non-obese (BMI <30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) participants, respectively. After controlling for total energy intake, BMI, and insulin level, total MET ($\beta = -0.428$, $P < 0.001$) was negatively associated with leptin gene expression in visceral adipose tissue among obese participants; however total MET was not significantly related to leptin gene expression in subcutaneous adipose tissue. Besides, MET related home ($\beta = -0.316$, $P = 0.035$) and leisure time ($\beta = -0.651$, $P < 0.001$) were negatively associated with visceral adipose tissue leptin gene expression.
Conclusions
Physical activity is negatively related to leptin gene expression in visceral adipose tissue participants with obesity only and this association is independent of fasting plasma insulin. This finding exaggerated the crucial role of PA to control of the development of obesity.

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Obesity

P530

Anti-insulin resistant effect of ferulic acid in high-fat diet-induced obese mice

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This study investigated the action of ferulic acid (FA) on the regulation of insulin sensitivity in high-fat diet (HFD)-induced obese mice. The ICR mice were fed with HFD (45 kcal% lard fat) for 16 weeks. Over the last 8 weeks of HFD feeding, these obese mice were orally administered with FA at doses of 25 and 50 mg/kg/day. At the end of all treatments, the epididymal fat, pancreas and hypothalamus were removed for analysis of biochemical parameters and expression of proteins. FA treatment significantly decreased leptin levels in fat tissue and the insulin levels in pancreas. Interestingly, treatment with FA improved the insulin sensitivity in hypothalamus, and up-regulated the expressions of insulin receptor substrate-1 (IRS-1), phosphatidylinositol-3 kinase (PI3K), and phosphorylated-protein kinase B (Akt) in obese mice. The histological examination showed smaller size of pancreatic islets in obese mice treated with FA compared to untreated obese mice. Overall, this study demonstrated the potential effect of FA for improving insulin function in HFD-induced obese mice. This effect is probably mediated via modulating the PI3K/Akt pathways.
Key word: Ferulic acid, insulin sensitivity, obesity

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P531

Non-alcoholic fatty liver disease and its association with insulin resistance in an obese population

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Background and aims
Obesity induced inflammation is a key component in the pathogenesis of insulin resistance (IR). In addition, obesity-related non-alcoholic fatty liver disease (NAFLD) also seems to contribute to IR development. Until now, however, it is unclear which, if any component of NAFLD specifically associates with IR. Therefore, the aim is to assess if individual components of NAFLD contribute to IR in obese patients undergoing gastric bypass surgery (GBS).
Subjects and methods
This cross-sectional study included 62 obese patients (mean age 45 ± 10 years; BMI 41.7 ± 4.5 kg/m^2) undergoing GBS and 62 healthy, age-matched control subjects (mean age 45 ± 10 years; BMI 23.5 ± 1.8 kg/m^2). Glucose levels were analysed by hexokinase method and insulin levels with electrochemiluminescence. Homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated with following formula HOMA-IR = {fasting glucose (mmol/l) * fasting insulin (μU/ml)}/22.5. Liver biopsies taken during GBS were evaluated using NASH-CRN scoring system (NAS score) and Steatosis, Activity and Fibrosis scoring (SAF score).
Results
GBS patients showed higher glucose, insulin and HOMA-IR levels (all $P < 0.001$) compared to controls. Among GBS patients, according to the SAF score, patients with non-alcoholic steatohepatitis (NASH) had higher glucose levels compared to those without. Besides, with an increasing grade of inflammation patients had higher HOMA-IR and insulin levels ($P < 0.05$), an association that is independent from age, BMI and cholesterol ($F(2,48) = 3309$; $P = 0.045$). Ballooning was not associated with HOMA-IR, insulin or glucose levels, whereas an association between steatosis grade and HOMA-IR levels was lost after controlling for age and BMI. An increasing grade of fibrosis was correlated with insulin and HOMA-IR levels ($r_s = 0.256$, $P = 0.048$ and $r_s = 0.255$, $P = 0.049$; respectively).
Conclusion
This study showed that within an insulin resistant group of obese patients, the level of IR correlates with histopathologic subcomponents of NAFLD. Specifically, whereas steatosis and ballooning are not associated with HOMA-IR, a higher grade of hepatic inflammation was associated with higher IR. For fibrosis, a trend toward higher IR with higher grade of fibrosis was found.

Whether this finding reflects a subgroup of patients with more severe adiposity-related consequences or whether this results from a direct effect of hepatic inflammation (and fibrosis) on IR needs to be further investigated.

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Using on-line program of good nutrition and wright diet may reduce the risks of diabetes mellitus in the future

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Objectives
It is too much easier and cheaper to combat obesity, than in the future to treat diabetes mellitus and its complications.
Methods
We used an online system for patient education (www.rightdiet.ru) based on the video lessons, full of humor, pictures, and cartoons to convey the necessary information on good nutrition, necessary to do exercises and the need for exposure to the sun to our patients.
Results
A patient was in touch with a doctor-endocrinologist in the case of any additional questions. We examined data from a survey of 650 patients registered in the online system and 100 patients control group who received the same recommendations on the appointment. The average weight loss was 7.3 kg in the main group. Regular physical activity was higher in the main group compared with the control one of 245 and 75 min per week respectively. Watching the short movies, the patients formed the habits of good nutrition during the first month already, which includes a diet with restriction of fat, digestible carbohydrates and daily consumption of low-fat dairy products, slow carbohydrates, protein and fiber. Were also presented recommendations for compliance with the physical activity, as well as vitamin D consumption.
Conclusions
Very important how we can make spreading of the material. Often the patient has no opportunity to go to the doctor for an appointment, and during the reception, it is not always possible to discuss all aspects, and even if it was possible, some information is forgotten by patients. So, we need to improve the quality of information material, including using online technologies to improve the quality and duration of life of our patients.

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P533

Effectiveness of bariatric surgery in metabolically healthy obese patients

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Objective
To evaluate the effectiveness and security of bariatric surgery in metabolically healthy obese (MHO).
Methods
A retrospective study of a cohort of all obese patients who underwent to bariatric surgery with a minimum two-year follow-up. Databases of all demographic, anthropometric and metabolic characteristics have been collected since 2007. Patients undergoing two surgeries were excluded. We defined as MHO patients those without diagnosis of diabetes or hypoglycemic treatment, basal blood glucose <5.6 mmol/l, HbA1c $<5.7\%$ and lipids (Tg <1.7 mmol/l and HDL $\geq =$ 1 mmol/l men/1.3 mmol/l women) no treated with fibrates. The statistical study was performed using SPSS version 24. Student's T test, Chi squared test, Pearson's correlation and multiple lineal regression were used.
Results
A total of 195 patients were included (mean age 48.8 ± 10.6 years, 68.7% of women) In 126 (64.6%) the surgical technique was the Gastric Sleeve whereas in 69 (35.4%) it was by-pass. Prior to surgery, 35 patients (17.9%) were MHO. Patients with MHO had a higher percentage of women compared with patients without MHO (82.9% vs 65.6% $P=0.046$) and a lower percentage of hypertensive patients (42.9% vs 57.1% $P=0.027$). In the second and third year post-surgery, MHO patients presented a higher % of excess body weight loss (%EBWL) (80.24% vs 69.52%, $P=0.010$ and 77.14% vs 63.66%; $P=0.015$, respectively). Multiple regression analysis showed that age and the presence of MHO inversely correlated with %EBWL. We did not detect any differences of acute complications after bariatric surgery.
Conclusions
Bariatric surgery in patients with MHO is associated with higher weight loss.

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The relationship between obesity, insulin resistance and conjunctival impression cytology

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Introduction
This study was designed to determine whether obesity causes inflammation on both conjunctival epithelium cells as well as on squamous metaplasia.
Materials and methods
Around 61 volunteer participants who had no previous history of illness or drug use were involved in this study. Of them, nearly 20 were obese, and 41 were of normal weight. We measured the glucose and insulin values for all volunteers. We also measured the Body Mass Index (BMI) and Homeostasis Model Assessment for Insulin Resistance (HOMA IR). The impression cytology method was used to analyze the conjunctival epithelium cells and classify them between Grades 0 to 3 according to the Nelson criteria.
Results
While there was a certain level of inflammation on the 90% of, as well as squamous metaplasia (Grade 2-3 inflammation) on the 80% of obese participants, the impression cytology was found to be normal only in two patients. The expected results were observed on the 56.1% of the control group, and the squamous metaplasia rate was nearly 17% ($P<0.001$). 90.9% of the patients with grade 3 inflammation were obese. The variables as independent predictors were found to indicate the existence of inflammation in conjunctivae at various levels; BMI (OR:1,24; $P=0.002$) and HOMA IR (OR $=28.6$; $P=0.001$) in a Model I multivariable regression model, and the existence of obesity (OR:11.91; $P=0.002$) and HOMA IR (OR $=15.08$; $P<0.001$) in a Model II multivariable regression model.
Conclusion
Obesity was found to be a disorder that causes inflammation on the conjunctival epithelium cells for the first time.

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Effect of the Andean plant Lampaya on NF-κB and JNK phosphorylation in human macrophages treated with palmitic acid.

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Background
Adipose tissue dysfunction occurring in obesity leads to a low grade chronic inflammatory state. Fat tissue from obese individuals has a high infiltration rate of

macrophages contributing to the development of obesity-related inflammation. At the cellular level, inflammation can be triggered by the activation (phosphorylation) of NF-κB as well as JNK. On the other hand, palmitic acid (PA) is a saturated fatty acid found elevated in plasma from obese subjects and shows pro-inflammatory activities in different cell types. Interestingly, people living in the Andean High Plateau in Northern Chile use the plant *Lampaya medicinalis* Phil. (Verbenaceae), known as Lampaya, against inflammatory diseases (rheumatism, arthritis and joint pain). The aim of this study was to evaluate the effect of a hydroalcoholic extract of Lampaya (HEL) against PA- induced inflammation in cultures of human macrophages.
Methods
Macrophages of the cell line THP-1 were incubated for 18 h in the following conditions: i) Control, ii) 0.1 μg/ml HEL, iii) 10 μg/ml HEL, iv) 0.2 mM PA, v) 0.1 μg/ml HEL +0.2 mM PA, vi) 10 μg/ml HEL +0.2 mM PA. Cell viability was determined by Tripan blue exclusion and phosphorylation of JNK and NF-κB was evaluated by Western blot.
Results
0.1 and 10 μg/ml HEL did not affect cell viability compared to the control condition. PA-treated cells showed a 40% reduction in cell viability compared to control. Interestingly, when macrophages were treated with PA plus 0.1 μg/ml or 10 μg/ml HEL viability was restored to the control condition. On the other hand, a 40% increase in NF-κB phosphorylation was found in PA-treated macrophages compared to vehicle-treated cells. JNK phosphorylation was comparable between all experimental conditions assessed. In macrophages co-treated with HEL and PA, NF-κB phosphorylation was comparable to the control condition.
Conclusions
HEL overcomes PA-induced reduction in cell viability as well as the increase in NF-κB activation in THP-1 macrophages. These findings might support the traditional use of the plant for treating pathologies with an inflammatory component, such as the metabolic diseases associated with obesity.

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The effect of n-3 PUFA on lipid profile, inflammation and insulin resistance

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Insulin resistance, lipid imbalance and inflammatory process have deleterious effect on cardiovascular system. Omega-3 polyunsaturated fatty acids (n-3 PUFA) (Docosahexaenoic acid [DHA] and Eicosapentaenoic acid [EPA]) are lipids that have beneficial effects. Our objective was to study the effects of n-3PUFA on anthropometric characteristics, inflammation, lipid profile and insulin resistance of the children with obesity.
Materials and methods
Thirty obese children aged 8–18 year with body mass index (BMI) >95% for their age and gender were enrolled into the study. After clinical evaluation and sample collection, patients were treated with 1250 mg of n-3 PUFA containing EPA 425 mg and DHA 325 mg, once a day for three months. Anthropometric characteristics were measured and BMI was calculated. Fasting blood glucose, insulin, CRP and lipids were measured in fasting blood samples before and after intervention. $P<0.05$ was considered significant.
Results
Treatment with n-3 PUFA did not have any significant effect on anthropometric characteristics including BMI, waist and hip circumference and waist to hip circumference ratio. Serum CRP level changed from 2.85 ± 1.65 mg/dl to 1.3 ± 1.03 mg/dl which significantly showed decreased inflammation in response to n-3 PUFA administration ($P<0.001$). In lipid profile, blood triglyceride was changed from 117.5 ± 70.4 mg/dl to 91.8 ± 42.2 ($P=0.01$) and LDL-C from 91.3 ± 20.6 to 81.8 ± 20.6 ($P<0.001$). HDL-C was 42.76 ± 9.2 and reached to 47.14 ± 9.6 ($P=0.05$). Homeostasis model assessment (insulin resistance) (HOMA-IR) changed from 5.14 ± 3.1 to 4.11 ± 2.5 ($P=0.04$).
Conclusion
Short term administration of omega 3 fatty acids decreased insulin resistance and inflammation, changed lipid profile in better conditions but did not change anthropometric characteristics of obese children in short duration of study.

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Differences in adipocyte size and adipogenic potential in metabolically healthy and unhealthy obese bariatric surgery patients

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Introduction
The adipocyte expansion is a critical process with implications in the pathogenesis of metabolic syndrome and insulin resistance associated to obesity. Impaired adipogenesis leads to dysfunctional, hypertrophic adipocytes, chronic low grade inflammation and insulin resistance.
Methods
Our study included 18 obese patients (13 females and 5 males) mean age 38.76 ± 8.89 years and mean body mass index 46.06 ± 6.48 kg/m2, referred for Laparoscopic Sleeve Gastrectomy procedure. Patients were divided in metabolic healthy obese, MHO (6 patients)and metabolic unhealthy obese, MUHO (12 patients) according to IDF criteria. Antropometric measurements, biochemical and hormonal profile were evaluated. Subcutaneous adipocyte size was assessed using Adiposoft software on microscopic images of formalin fixed adipose tissue. The subcutaneous adipose derived stromal/stem cells (ASCs) were isolated and the mesenchymal origin was demonstrated by cytoskeleton vimentin fluorescent staining. To evaluate the adipogenic capacity of these precursor cells derived from obese patients, the ASCs were grown to confluence and differentiated *in vitro* for 21 ± 3 days using an adipogenic protocol. We evaluated the lipid accumulation in mature adipocytes by specific lipid dye(Oil Red O). Spectrophotometric analysis of the lipid stain was used to quantify the lipid accumulation and fluorescent nuclear dye with DAPI was used for accurate cell count of mature adipocytes.
Results
Mean adipocyte area was significantly lower in MUHO as compared to MHO($P<0.05$) The lipid accumulation in mature adipocytes obtained by isolation, proliferation and differentiation of subcutaneous ASCs was between 12.5% and 108.76%, being significantly higher in the MUHO group($P<0.05$) as compared to MHO. For both groups, significant correlations was found between lipid accumulation and HOMA-IR ($P=0.01$), C peptide ($P<0.05$) and morning cortisol levels ($P<0.05$). No significant correlation was found between lipid accumulation and age or body mass index (BMI).
Conclusion
The evaluation of subcutaneous adipocyte size and adipogenic potential of ASCs derived from subcutaneous adipose tissue could be a good predictor of the metabolic risk for obese patients.

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Glucocorticoid positively regulate Agouti-related protein gene

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Purpose
Glucocorticoid is one of the key hormones that regulates energy balance. Glucocorticoid excess induce hyperphagia and obesity (e.g. Cushing syndrome), however, its mechanisms are not fully elucidated. On the other hand, Agouti-related protein (AgRP) is known as an orexigenic neuropeptide, which is expressed in the hypothalamic arcuate nucleus. To clarify the role of Agouti-related protein (AgRP) in glucocorticoid-induced obesity, we investigate here the effect of glucocorticoid on AgRP gene transcription and expression.
Methods
We examined *in vitro* the effect of dexamethasone on the AgRP gene transcription using the reporter assay and the electromobility shift assay (EMSA) in BE(2)C cells. We also examined *in vivo* the effect of corticosterone (CORT) administration on hypothalamic AgRP mRNA in C57BL6 mice using real time PCR.
Results
There are two glucocorticoid responsive elements (GRE1 and GRE2) in AgRP 5'-promoter region. Dexamethasone robust increased AgRP transcriptional

activity. Deletion analysis revealed that GREs were necessary for dexamethasone responsiveness, and binding of glucocorticoid receptor to GREs was confirmed by the EMSA. CORT administration (2 weeks) increased body weight, food consumption and hypothalamic AgRP mRNA expression (AgRP/GAPDH:placebo 100.0±9.9, CORT 133.2±8.4, $P<0.05$).
Conclusion
These results suggest that glucocorticoid positively regulate AgRP gene transcription and expression. Glucocorticoid-induced hypothalamic AgRP could be associated with hyperphagia and obesity in Cushing syndrome.

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Relationship between body image perception, diet trial and depression in Korean adults: Korea National Health and Nutrition Examination Survey 2014

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Introduction
Previously we investigated the relationship between obesity and depression in Korean adults using data from a population-based sample from the 2014 Korea National Health and Nutritional Examination Survey (KNHANES) by cross-sectional study. We further investigated about relationship between body image perception, diet trial and depression in -depth study.
Methods
In total, 4,026 subjects (1,692 men, 2,334 women) aged 19–69 years participated in the 2014 KNHANES. Current depression was defined as a score ≥10 on the nine-item Patient Health Questionnaire (PHQ-9). Height and weight were measured and the body mass index (BMI) was calculated. The participants were asked to complete questionnaires about socio-demographic factors and disease comorbidities, and health-related behaviors. The chi-square test and multivariate logistic regression analyses were performed to examine the relationship between obesity, body image perception, diet trial and depression.
Results
According to body weight status, there was a significant difference in the prevalence of depression (underweight: 16.2%, normal weight: 5.5%, overweight: 4.3%, obese [BMI≥30]: 6.9%). Compared to the normal weight group, the underweight group had a higher adjusted odds ratio (OR) for depression (OR = 3.34, 95% confidence interval [CI]: 2.18, 5.11). For underweight group, when they had body image perception that they are thin or obese, they had higher PHQ-9 scores for depression ($P=0.001$) and only when they had body image perception that they are thin, they had depression (16.2%). For overweight group, only when they had body image perception that they are obese, they had depression (4.3%). For obese group, none of them had depression who had body image perception that they are obese (0%). For groups who tried to loose weight, exercise group had no depression while fasting, skipping meals or taking diet pills group had depression ($P=0.01$).
Conclusions
This study shows differences in the risk of depression depending upon body weight status. Being underweight was correlated with a high risk of developing depression in both men and women in regard to their body image perception as thin or obese. For groups trying to loose weight, exercise may be a better way than fasting, skipping meals or taking diet pills for their mental health.
Keywords: Body mass index, Body image, Depression,

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Obstructive sleep apnea syndrome frequency in obese patients

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Introduction
Obstructive sleep apnea syndrome (OSAS) is a common disorder whose prevalence is linked to an epidemic of obesity. OSAS is caused by recurrent episodes of upper airway obstruction during sleep, leading to reduction or cessation of the airflow. Studies have shown a strong association among OSAS and cardiovascular morbidity and mortality. Therefore, currently we performe overnight polysomnograpy in all patients with obesity in our outpatient clinic. In order to observe the results, we retrospectively analyzed the polysomnography results of 54 patients with obesity who were followed-up in our outpatient clinic.
Results
Medical records of 54 patients with obesity [22 male and 32 female, mean age 54.5±9.0 and mean Body Mass Index (BMI) of 41±8.0 kg/m^2].The mean age and BMI between male and female patients were not significantly different [55.6±9.0 and 38.3±6.0 kg/m^2; 53.8±8.7 and 41.3±8.8 kg/m^2, respectively ($p>0.05$)]. OSAS was detected in 49 of 54 (90%) patients. Mean BMI was 41.4±8.4 and 35.6±2.9 kg/m^2 in obese patients with and without OSAS, respectively ($P=0.02$). In their medical records, 44 of 49 patient with OSAS were found to be classified according to the severity of OSAS (5 of them were not determined severe or not). These 44 patients with OSAS were divided into 3 subgroups including mild, moderate and severe, according to the severity of OSAS. In this study, 9,11 and 24 patients with mean BMI of 43.7, 38.7 and 43.2 kg/m^2 had mild, moderate and severe OSAS, respectively.No correlation was found between the severity of OSAS and BMI in our study ($P>0.05$).
Conclusion
Although OSAS was more common in patients with BMI of >35 kg/m^2, the severity of OSAS was not related to higher BMI levels. Other confounding factors rather than BMI should be taken in consideration during the assessment of the severity of OSAS.

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P541

Impact of bariatric surgery on working productivity in patients with morbid obesity

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Introduction
Morbid obesity (MO) is a major global public health problem, associated with a significant economic burden, both due to its high prevalence and the number and severity of its comorbidities. MO is associated with a high degree of difficulty to lead a normal social and working life. Weight loss is effective in decreasing these risks and to reduce disease severity. Bariatric surgery (BS) is an effective therapy for sustained weight loss and for the improvement of the quality of life of these patients. Nevertheless, data in literature is scarce regarding the impact of BS on the working productivity (WP) of the MO patients. On these bases, the objective of the present study is to evaluate the relationship between BS and WP in MO patients.
Methods
We performed a retrospective revision of the medical records of the consecutive patients that attended the MO Unit of our center between February-October 2017 and had a complete psychological evaluation. The specific psychological exam in the MO Unit was performed using the ZKPQ, STAI, BDI-II, BITE and Rosenberg SS questionnaires as part of the pre-BS evaluation as per protocol. On the day of the visit to our center, the WPAI-GH questionnaire was administered to all the patients.
Results
138 patients were recluted, aging 48.21±10.81 years, 73% women, and 85.4% Caucasian. A total of 56.2% were not employed. 61.03% of the cases underwent BS, with a follow-up of 36.45±27.82 months and a satisfactory evolution (previous BMI 44.12±6.8 kg/m^2 vs post-BS BMI 33.4±5 kg/m^2, $P<0.001$). In the group of BS patients, 83.0% were not previously employed and 3.03% have been reinserted into the labor market after the BS. No significant correlations were found between the WP and the age, gender, ethnicity, any BMI, MO related comorbidities, follow-up time after the BS, surgical technique or socio-economic status. We found significant correlations between the WP and the education level, the presence of depression, anxiety and lack of activity as well as self-esteem evaluated by the psychological tests previous BS.
Conclusion
A significant percentage of patients with MO that underwent BS were not employed, despite the satisfactory evolution in terms of BMI. A significant correlation exists between the WP and the pre-BS psychological profile of the MO patients.

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Associations of circulating adipokine levels with metabolic risk factors and renal function in a general population

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Background, objective
Adipose tissue is known to secrete a multitude of bioactive adipokines and it seems that the majority of these adipokines is implicated in the pathogenesis of obesity and associated metabolic diseases. Existing research studies mostly concentrated on one or two adipokines and therefore, comparisons of the involvement of different adipokines in these disorders are difficult. Furthermore, associations of circulating adipokine levels with different fat compounds or lifestyle factors are mostly missing in existing studies. This study aimed to provide a comprehensive overview of the associations of a panel of circulating adipokines (adiponectin, leptin, resistin, chemerin, vaspin) with metabolic parameters and renal function in a well characterized large population-based study.
Methods
Data from 4129 subjects of the Study of Health in Pomerania were analyzed. Residual method was used to investigate the associations of MRI-quantified liver fat content as well as visceral (VAT) and subcutaneous adipose tissue (SAT) with circulating adipokine levels. Furthermore, multivariable regression models were applied to examine the associations of adipokine concentrations with lifestyle factors (smoking, alcohol consumption, physical inactivity), metabolic phenotypes, and renal function.
Results
Independently of other fat compounds, liver fat content, SAT, and VAT were inversely associated with adiponectin. Furthermore, an independent positive association of liver fat content and SAT with chemerin was observed. The strongest independent association was detected between SAT and leptin. Physically inactive subjects had higher chemerin and leptin levels and smoking led to higher chemerin as well as lower adiponectin and leptin concentrations. Alcohol consumption was associated with adiponectin (positive) and resistin (inverse). Obese subjects showed increased chemerin, leptin, and vaspin levels, but decreased adiponectin concentrations. All adipokines were associated with lipid markers, whereas associations with parameters of glucose metabolism were only seen for adiponectin, chemerin, and leptin. An inverse association of similar strength was observed between chemerin, leptin as well as resistin and estimated glomerular filtration rate (beta -0.2, $P<0.01$).
Conclusion
Our results indicate that the associations between different circulating adipokine levels and metabolic risk factors as well as renal function significantly differ. In general, high adiponectin levels seem to have a protective role whereas increased chemerin, leptin, resistin, or vaspin concentrations seem to be disadvantageous for the investigated alterations. Leptin concentrations play a key role during obesity, whereas for other metabolic disorders adiponectin and chemerin levels seem to be more meaningful. During processes of renal disease circulating chemerin, leptin, and resistin levels might be of similar importance.

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P543

Association of sleep duration and obesity according to sex and age in Korean adults: results from the Korea national health and nutrition examination survey 2007–2015

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Background/objectives
This study aimed to investigate associations between self-reported sleep duration and general and abdominal obesity in Korean adults stratified according to sex and age.
Subjects/methods
Data from 41,805 adults, 18–110 years of age, collected by the Korean National Health and Nutrition Examination Survey (KNHANES) in 2007 and 2015, were included. Obesity was defined as body mass index (BMI) ≥ 25 kg/m^2, and abdominal obesity as waist circumference ≥ 90 cm in men and ≥ 85 cm in women. To control for sociodemographic and lifestyle factors and comorbidities, multivariable logistic regression was used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for obesity and abdominal obesity across sleep duration categories of ≤ 5, 6–8, and ≥ 9 h/day.
Results
The mean ($\pm$ S.E.M.) age was 43.8 ± 0.13 years; BMI was 23.7 ± 0.02 kg/m^2; waist circumference was 81.1 ± 0.08 cm; and sleep duration was 6.9 ± 1.3 h/day. General obesity was present in 13,203 (31.7%) participants and abdominal obesity in 10,712 (23.9%). Among individuals 30–49 years of age, there was an increased adjusted OR for obesity only for sleep duration ≤ 5 h/day compared with sleep duration 6–8 h/day, both in men (OR 1.25 (95% CI 1.02–1.54)) and women (OR 1.56 (95% CI 1.29–1.90)), after controlling for sociodemographic and lifestyle factors. Regarding women, there was increased adjusted OR for abdominal obesity for sleep duration ≤ 5 h/day (OR 1.45 (95% CI 1.18–1.78)) and ≥ 9 h/day (OR 1.38 (95% CI 1.09–1.76)) compared with sleep duration 6–8 h/day. However, for elderly individuals (≥ 65 years), there was a negative association between sleep duration ≤ 5 h/day and obesity, but not with abdominal obesity, in both men and women.
Conclusion
This study demonstrated a significant association between sleep duration and obesity, which varied according to sex and age.

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P544

Relation of serum irisin levels, non-alcoholic fatty liver disease, glucose and lipid metabolism parameters in obese children

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Irisin is a myokine induced by exercise, that converts white fat tissue to brown fat tissue, thereby increasing thermogenesis and providing energy expenditure. The aim of this study is to determine the relationships between serum irisin levels and glucose and lipid parameters in obese children with and without non-alcoholic fatty liver disease (NAFLD). A total of 60 pubertal obese children (31 F, 29 M, age range: 11–18 yrs.) were included in this study. 30 of Whom had NAFLD. The control group consisted of 28 healthy children (14 F, 14 M) who were similar in age and sex to the obese group.
Results
The median serum irisin level was lower in the obese group (5.26 μg/ml (4.2–6) μg/ml) than in the control group (7.5 μg/ml (6.5–9) ($P<0.05$). The median irisin levels in both patients with NAFLD (5.7 μg/ml (4.6–6.5) and without NAFLD (5 μg/ml (3.9–5.7) were lower than the control group's ($P<0.05$). Serum irisin levels were not different between patients with and without NAFLD ($P>0.05$). According to the presence of insulin resistance in the obese group, irisin levels did not change ($P>0.05$). In the obese group, irisin were correlated with BMI, waist and arm circumfrence. In the whole study group, serum irisin levels correlated negatively with BMI, waist, hip and arm circumferences, waist/hip ratio, skinfold thickness (triceps and biceps) and AST, ALT levels. There were no correlations between serum irisin levels and LDL-C, triglyceride and total cholesterol, but a positive correlation was found with HDL-C. Consequently, low serum irisin levels are found in obese children. It is not different between patients with and without NAFLD. Irisin levels are correlated negatively with fat tissue parameters and ALT-AST levels. Low irisin levels may be related to the presence of decreased muscle mass and/or decreased brown adipose tissue and hepatic injury in obesity.

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P545

Do dietary acidic and basic amino acids intake play role in FTO gene expression among non-diabetic adults?

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Introduction
The fat mass and obesity-associated gene (FTO) has been shown to be associated with obesity and might be affected by dietary factors. Long-term dietary intake of amino acids are capable to change adipose tissue metabolism through regulation of FTO production. This study aims to examining the association of dietary acidic and basic amino acids (AAs) with FTO gene expression in subcutaneous and visceral adipose tissues among non-diabetic adults.
Methods
A total of 87 adults (23% men), who were free of diabetes and undergone open abdominal surgery were included. Average intakes of acidic AAs including glutamic and aspartic acid, and basic AAs including histidine, arginine, and lysine were collected using a valid and reliable semi-quantitative food frequency questionnaire. During the surgery visceral and subcutaneous adipose tissues were obtained, and FTO gene expression of both fat depots were assessed by Real-Time PCR.
Results
Mean (S.D.) for BMI among obese and non-obese participants were 42.6 (7.3) and 25.3 (3.1) kg/m^2, respectively. The median (25–75 IQR) intake of acidic and basic AAs were 9.7 (6.5–12.0) and 19.8 (25.1–13.7) g/d, which included 9.6 and 18.7 percent of total daily protein intake, respectively. No significant difference was observed for FTO gene expression in subcutaneous (-0.518 vs. 0.395, $P=0.471$) and visceral (-0.999 vs 0.773, $P=0.161$) fat mass between non-obese and obese participants, respectively. After adjusting for BMI and energy intake, 1-gram increment in acidic and basic AAs were accompanied with -0.358 ($P=0.019$) and -0.308 ($P=0.045$) unit increase in subcutaneous and -0.339 ($P=0.017$) and -0.320 ($P=0.020$) unit decrease in visceral FTO gene expression among obese participants, respectively. However, no significant association of acidic and basic AAs intake with neither subcutaneous (($\beta=0.088$, $P=0.632$) and ($\beta=0.119$, $P=0.518$), respectively) nor visceral (($\beta=0.232$, $P=0.257$) and ($\beta=0.230$, $P=0.257$), respectively) adipose tissue were found among non-obese participants.
Conclusion
Our finding showed that higher dietary acidic and basic AAs can decrease FTO gene expression among obese non-diabetic adults.

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P546

Long term dietary intake of aromatic amino acids are associated with leptin gene expression in adipose tissues of non-diabetic adults

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Introduction
Among the adipokines, leptin is one of the hormones directly connects to body fat and obesity. Investigating the impacts of dietary amino acids on adipose tissue metabolism have emerged as a fascinating area for researchers which they reported that dietary amino acids can affect and regulate gene activity in adipose tissues both directly and indirectly, with positive or negative effects.
Methods
Visceral and subcutaneous adipose tissues were gathered from 98 non-diabetic participants aged ≥ 20, who had undergone elective abdominal surgery. Average intakes of AAAs including phenylalanine, tyrosine, and tryptophan were collected using a valid and reliable food frequency questionnaire. The leptin gene expression in visceral and subcutaneous adipose tissues was measured by Real-Time PCR.
Results
Mean (S.D.) age and AAA intake of participants (23% male) were 41.7 (14.2) years and 7.38 (3.7) g/day, respectively. Total AAA intakes in ranking order were phenylalanine 3.9 g (the highest), followed by tyrosine 2.3 g, tryptophan 3.3 g, corresponding to 3.7%, 2.1%, and 2.9% of total protein intakes, respectively. No significant difference was observed for leptin gene expression in subcutaneous (-0.135 vs 0.791, $P=0.992$) and visceral (-1.582 vs 0.915, $P=0.891$) fat mass between non-obese (BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) participants, respectively. After controlling for BMI and energy, dietary intake of dietary AAA ($\beta=0.404$, $P<0.001$), phenylalanine ($\beta=0.522$, $P<0.001$), tyrosine ($\beta=0.224$, $P=0.081$), and tryptophan ($\beta=0.520$, $P<0.001$) was positively associated with subcutaneous adipose tissues leptin gene expression among obese participants. Besides, a significant positive association of dietary AAA ($\beta=0.513$, $P<0.001$), phenylalanine ($\beta=0.399$, $P<0.001$), tyrosine ($\beta=0.234$, $P=0.078$), and tryptophan ($\beta=0.430$, $P=0.001$) with leptin mRNA from visceral adipose tissue were observed. Among non-obese participants, none of the AAA showed significant association with leptin gene expression in both adipose tissues.
Conclusion
Habitual intake of phenylalanine, tyrosine, and tryptophan were associated with leptin gene expression in visceral and subcutaneous adipose tissues, suggesting an important role of quality proteins intake in adipose tissue to regulate leptin expression.

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P547

Assessment of macrophage apoptosis inhibitor (AIM), monocyte chemotactic protein-1 (MCP-1) and C reactive protein (CRP) levels in patients with metabolic syndrome

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Metabolic syndrome is an important health problem that has been shown to be associated with cardiovascular disease and mortality. Recent studies have shown the importance of inflammation in visceral fat tissue. Macrophage apoptosis inhibitor (AIM) and monocyte chemotactic protein (MCP-1) are molecules that cause migrating to visceral fat tissue of M1 macrophages that initiate adipocyte inflammation. The aim of this study is to understand the role of these molecules in the pathogenesis of the syndrome and to investigate whether they can be used as biomarkers in the diagnosis. For this purpose, 40 metabolic syndrome patients and 40 healthy individuals who were referred to Hacettepe University Hospital were included in the study. The mean age was higher in the metabolic syndrome group (46.68.8 and 40.37.9, $P=0.003$) when there was no gender difference between the groups. Serum AIM, MCP-1 and CRP levels were significantly higher in the metabolic syndrome group ($P<0.01$, $P<0.01$ and $P<0.05$). There was a significant positive correlation between serum AIM, MCP-1 and CRP levels with waist circumference ($r=0.480$, $r=0.663$ and $r=0.418$, $P<0.01$). ROC analysis was performed to determine the best cut points that could be used in the diagnosis of the metabolic syndrome. The area under curve (AUC) of the serum AIM MCP-1 and CRP cut off points (2383.7 pg/ml, 172.8 pg/ml and 0.366 mg/dl) that could be used in the diagnosis of the metabolic syndrome has been found statistically significant (AUC for AIM is 0.767, for MCP-1 is 0.651 and for CRP is 0.907, $P<0.05$). In addition, serum AIM and CRP levels above cut-off point, were independent risk factors for metabolic syndrome, whereas serum MCP-1 level was not independent risk factor. In conclusion AIM and MCP-1 may be effective molecules in the pathogenesis of metabolic syndrome and its subgroups. Serum AIM, MCP-1 and CRP levels can be used as a biomarker for diagnosis of metabolic syndrome.

	MS (+) $n=40$	MS (−) $n=40$	P
AIM (ng/ml)[a]	2506 (1212–4386)	1912 (1168–3564)	0.001
MCP-1 (pg/ml)[b]	178.2 (54.3)	150.3 (45.7)	0.016
CRP (mg/dl)[a]	0.60 (0.15–1.78)	0.20 (0.1–0.59)	0.001

[a]Mann Whitney U test, median (min–max)
[b]Independent group T test mean (±S.D.)

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P548

Oxidized low-density lipoprotein (oxLDL) as a possible biomarker of cardiovascular diseases in obese subjects

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Introduction
oxLDL are produced from the oxidation of low density lipoprotein (LDL) by macrophages and endothelial cells, becoming cytotoxic and immunogenic. They are also a potent inhibitor of the macrophages mobility, contributing to the vascular wall progressive inflammatory infiltration and atherosclerosis formation. Weight loss can prevent atherosclerotic plaque progression of and acute coronary events in obese subjects, so that oxLDL could be used a biomarker of cardiovascular diseases.
Objective
- To study oxLDL levels in patients with morbid obesity and lean subjects, as well as analyzing changes in oxLDL levels in patients with morbid obesity after significant weight loss due to bariatric surgery.

Methods
- No randomized clinical trial.
- 68 patients with morbid obesity and 31 healthy subjects with normal weight.
- Variables studied: BMI (kg/m^2), waist-hip ratio (WHR), systolic and diastolic blood pressure (SBP and DBP, mmHg), total cholesterol (TC, mg/dl), LDL (mg/dl), high density lipoprotein (HDL, mg/dl), triglycerides (TG, mg/dl), high-sensitivity C-reactive protein (hs-CRP, mg/l) and oxLDL (mg/dl).
- Obese patients underwent gastric bypass surgery and, after 12 months and major weight loss, the same variables were reassessed.

Results
We found a statistically significant difference in plasma levels of oxLDL in the group of morbidly obese 1.28 ± 0.39 mg/dl compared with subjects with normal weight 1.13 ± 0.26 mg/dl ($P = 0.038$). In obese patients 1 year after surgery and after a significant weight loss, SBP, DBP, TC, LDL, TG and hs-CRP levels significantly decreased, and HDL levels increased significantly. Despite this, the oxLDL values did not vary significantly with respect to the baseline, with levels of 1.26 ± 0.37 mg/dl. When dividing the obese patients into two groups based on the median of oxLDL (1.19 mg/dl), it was found that in the group with oxLDL levels above the median there was a significant decrease one year after surgery (1.55 ± 0.34 vs. 1.36 ± 0.33 mg/dl, $P = 0.01$).
Conclusion
Significant differences between oxLDL levels among morbid obesity patients and healthy subjects were found, although the levels did not decrease after weight loss despite the improvement in the lipid profile experienced, SBP, DBP and the decrease in hs-CRP. However, oxLDL levels decreased in obese patients with higher levels of oxLDL before surgery, so that oxLDL could be a biomarker in cardiovascular diseases, but not in early stages of it.

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P549

Effects on comorbidities and safety of bariatric surgery in morbid obesity patients

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Objectives
1) To determine the prevalence on the main comorbidities in morbid obese patients; 2) To analize the bariatric surgery effects on the comorbidities; and 3) To evaluate the complications of bariatric surgery
Methods
Cohort study with intrasubject measures (before-after) in a sample of 333 patients with morbid obesity who underwent bariatric surgery (bypass gastric or sleeve gastrectomy) in Puerta del Mar Hospital (Cádiz, Spain) between 2005 and 2015. Demographic characteristics, anthropometric parameters, cardiovascular risk factors and surgical complications were analyzed baseline and two years after surgery.
Results
A total of 333 patients were included (71.5% female), with mean age 40.05 ± 9.98 years. The mean preoperative BMI was 50.21 ± 6.98 kg/m^2. Before surgery 26.45% were smokers, 42.3% had hypertension, 45% dyslipidemia and 26.3% diabetes. 5.1% of patients underwent bypass gastric and 44.9% sleeve gastrectomy. After 2 years of follow up, the percentage of weight lost was 69.16%. Remission of hypertension, dyslipidemia and diabetes mellitus type 2 had occurred in 68.4%, 75.5% and 77.6% respectively ($P < 0.001$). Levels of HbA1c, cholesterol and trygliceridemia were reduced significantly after surgery. 12% of patients had early complications and 17.5% developed later complications (The most frequent complication was eventration).
Conclusions
Bariatric surgery in our area is an effective tool in weight loss. It is related with early beneficial effects on metabolic disorders and have similar rate of surgical complications compared with other series.

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P550

Association of total antioxidant capacity and p53 mRNA levels in subcutaneous adipose tissue of obese subjects

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Objective
Dietary total antioxidant capacity (TAC) has been assumed as a useful tool to consider the relationship between the cumulative antioxidant food capacity and several chronic disorders. The contribution of p53 to many aspects of age-associated diseases, such as cardiovascular and metabolic disorders has been recognized. The role of dietary TAC in adipose tissues metabolism especially its association with P53 gene expression is not established yet in fat mass. The aim of the study was to investigate the association of dietary TAC intake with p53 gene expression in omental and subcutaneous adipose tissues of obese and non-obese adults.
Methods
In this cross-sectional study, omental and subcutaneous adipose tissues of 98 non-diabetic participants including 44 subjects with BMI < 30 and 54 subjects with BMI ≥ 30 kg/m^2 were collected from who had undergone elective abdominal surgery. Usual intake of participants was assessed by a relative and validated semi-quantitative food-frequency questionnaire (FFQ) before the surgery. Dietary TAC intake was assessed based on the oxygen radical absorbance capacity method. The p53 gene expression was measured by using SYBR Green Real-Time PCR.
Results
The mean age of non-obese and obese participants was 46.3 ± 15.3 and 37.9 ± 11.6 years, respectively, which was significantly different ($P = 0.003$). The dietary TAC intake was 317.6 and 288.7 μmolTE/100g in obese and non-obese participants, respectively ($P = 0.434$). The mRNA levels of p53 in subcutaneous adipose tissues was 0.77 ± 4.84 and -0.06 ± 4.61 in obese and non-obese participants, respectively ($P = 0.397$) and in omental adipose tissue was -0.23 ± 4.50 and 1.35 ± 4.00 in obese and non-obese ones, respectively ($P = 0.078$). After controlling for age and total energy intake, TAC positively associated with subcutaneous adipose tissue p53 mRNA levels in obese participants ($B = 0.274$, $P = 0.043$). There was no significant association in omental adipose tissues ($B = 0.005$, $P = 0.974$).
Conclusion
Higher intake of TAC in the regular diet was associated with p53 gene expression in the subcutaneous adipose tissue; supporting this idea, that overall antioxidant capacity of diet is by affecting the intracellular concentration of p53 protects one from the development of carcinoma.

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P551

Influence of lifestyle modification on leptin and insulin resistance to prevent type 2 diabetes mellitus development

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The aim of the present study was to determine the change of fasting serum leptin and insulin levels and insulin resistance in patients with risk factors of diabetes mellitus of type 2 (DM 2) including impaired glucose tolerance/impaired fasting glucose (IGT/IFG).

Material and methods
The study included 100 patients (32 men, 68 female) 25–65 years old at risk factors of DM 2. All patients received recommendations on a balanced diet and physical activity. The average fasting plasma glucose (FPG), HbA1c, fasting serum leptin was detected by sensitive ELISA.
Results
During 18 months our study 56 patients carried out this recommendations (research group) and 44 patients did not (control group). Patients of the research group demonstrated mean reduction of body mass index (-2.6 ± 0.4 kg/m^2) and persons of the control group had significant increase of these parameters ($P<0.05$). Among subjects with IGT/IFG at baseline, glucose levels normalized in 56.0% of patients from the research group and 4.5% in control group ($P<0.001$). FPG and HbA1c in research group decreased from 11.9 ± 4.3 to 9.6 ± 4.5 μU/ml and from 6.4 ± 0.3 to 6.1 ± 0.3% accordingly ($P<0.05$). In control group the specified parameters had increased significantly ($P<0.01$). The serum leptin median in research group was decreased from 34.7 to 26.4 ng/ml (-23.9%, $P<0.001$) and increased in control group ($+17.9$%, $P<0.01$). The risk reduction of DM 2 development among patients of the research group was 48.0% compared to the control group.
Conclusion
Thereby, lifestyle modification can prevent the development of DM 2 in subjects with risk factors by reduction leptin.

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Postprandial glucose, insulin, and incretin responses to different type of breads in healthy overweight and obese individuals

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Background
Worldwide, bread is one of the most consumed foodstuff. White bread is made of white flour and process involves the exclusion of bran and embryo. On contrary, these are preserved in whole wheath. Compared the whole grain bread, most commercial white wheat breads contain little dietary fiber and it is assumed to cause more drastic rise and fall on glucose and insulin levels.
Objective
Aiming to investigate 3-hour effect of two different type of breads 21 volunteers (mean age: $37,6 \pm 6,4$ y); 10 overweight [(mean body mass index (in kg/m^2): $27,5 \pm 1,2$)] and 11 obese [(mean body mass index (in kg/m^2): $32,7 \pm 1,6$)] individuals with normal glucose tolerance were recruited into this study. The test products as indicated on Table 1 were whole-grain bread and white wheat bread. Each product provided 50 g available carbohydrate and was served in random order with breakfast with one-week intervals. Fasting and 3 postprandial blood samples were collected at intervals of 60 min for 3 h to determine plasma glucose, glucagon-like peptide 1 (GLP-1), serum insulin concentrations. Rates of increase in glucose and insulin levels of test breads were determined by calculating the area under the curve (AUC)
Results
While high GLP-1 levels was found on postprandial 120th minute, both glucose and insulin levels did not increase in the test with white bread at overweight individuals. On contrary at obese individuals glucose levels was found high level during 3 h and insulin levels was increased on 60th minute significantly ($P<0.05$) after consumption white wheat bread.
As a conclusion
White bread consumption is not healthy in society. Whole grain bread consumption should be recommended to obese people especially, in order to prevent their metabolic changes in their future lives.

Table 1 The nutrient contents of test samples containing 50 g of CHO

	White wheat bread	Whole grain bread
Carbohydrate (g/100 g)	50	50
Protein (g/100 g)	8.07	8.51
Fat (g/100 g)	1.53	1.61
Fiber (g)	5.61	8.68
Energy(kcal)	258	267

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The effects of bariatic surgery on clinical, renal parameters and urine ngal levels in diabetic and non-diabetic obese patients

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Background
It is known that obesity-related renal damage,regardless of type 2 diabetes and hypertension, may improve by weight-loss modalities. In this study, we aimed to evaluate the effect of bariatric surgery on glycemic and lipid parameters, anthropometric measurements, renal parameters and urine NGAL (Neutrophil Gelatinase-Associated Lipocalin) levels in obese diabetic or nondiabetic patients who has not respond to medical treatment
Materials and methods
In our study, laparoscopic sleeve gastrectomy was performed in 10 diabetic and 9 non-diabetic patients between the ages of 18–65, BMI ≥ 40 kg/m^2, who were approved by the bariatric surgery committee. Anthropometric measurements, biochemical values, and spot urine examination in preoperative and postoperative 6th week were obtained from the routine polyclinic examination. Urinary NGAL levels were measured with spectrophotometry using enzymatic immunoassay method.
Results
In general, a significant decrease in weight, BMI, fasting plasma glucose, fasting plasma glucose (FPG) and HbA1c values were found in the patients at 6th month after surgery compared to preoperative status ($P<0.001$, $P<0.001$, $P=0.003$, $P=0.001$, $P<0.001$). There was also a significant decrease in systolic and diastolic blood pressures and HOMA-IR values ($P=0.004$, $P=0.014$, $P=0.001$). There was also a significant decrease in triglyceride values ($P=0.005$), but there were no significant changes in LDL, HDL and total cholesterol. Serum creatinine was significantly decreased ($P=0.014$), but microalbumin (mAlb), mAlb/creatinine, NGAL and NGAL/creatinin values were not significantly changed. In the comparison of diabetic and non-diabetic cases, the decrease in FPG was significantly higher in the diabetic group ($P=0.005$), but there was no significant difference between the groups in terms of percentage changes of other parameters.
Discussion
Bariatric surgery is an effective method for the treatment of obesity and many related parameters. However, the pathogenesis of obesity-related renal damage has not yet been clarified and stronger data are needed to say that NGAL is a predictor of renal damage in the chronic period.

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P554

Abstract withdrawn.

P555

Are there differences in cardiovascular risk between metabolically healthy and sick obese?

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Introduction
Obesity is a major health problem and a risk factor for the development of other diseases. However, there are morbid obese subjects of long evolution that can be considered metabolically healthy obese, whose existence is in doubt for many clinicians.
Objetive
To analyze if there are differences in cardiovascular risk between metabolically healthy (MHO) and sick obese (MSO), matched by age, sex and body mass index (BMI).
Material and methods
We include patients who underwent bariatric surgery in our hospital. We divided them into two groups (MHO and MSO), matched by age (+/- 3 years), BMI (according to the obesity degrees) and by sex. The MHO were defined because they did not meet any criteria of the ATP III and because they did not have previous cardiovascular disease.
Results
164 patients were included. Basal characteristics were show in table 1. MHO had higher HDL level, lower triglycerides, glucose, HbA1c and lower values of systolic and diastolic blood pressure than MSO. The cardiovascular risk measured by Score was significantly lower in the MHO (0.04±0.19), than MSO (0.26±0.81), *P* 0.019). The same happened with the Framingham scale (MHO 0.04±0.190 vs MSO 4.04±3.66, *P* 0.001)

	MHO	MSO	P-value
Age (years)	38.46±10.40	38.57±10.21	0.946
Sex (♀ - ♂ %)	80.5 – 19.5	80.5 – 19.5	1
BMI (Kg/m^2)	50.51±8.45	50.38±7.64	0.916
Maximum weight (Kg)	136.89±22.35	140.22±28.85	0.348
Lost exccess wetht. (%)	59.81±22.59	56.47±23.12	0.378
Dyslipidemia (%)	0	19.6	0.001
Total colesterol (mg/dl)	175.42±34.61	176.49±39.43	0.855
HDL –c (mg/dl)	57.71±9.33	43.59±10.59	0.000
LDL –c (mg/dl)	109.26±28.08	118.46±35.06	0.066
Triglycerides (mg/dl)	90.07±30.70	115.44±6.76	0.002
DM (%)	0	34,3	0.001
Glucose (mg/dl)	89.62±7.70	105.35±38.74	0.000
HbA1c (%)	5.70±0.58	6.29±1.64	0.020
HTA (%)	0	36,6	0.001
TA S (mmHg)	119.19±8.14	128.79±19.06	0.000
TA D (mmHg)	71.68±6.62	78.33±13.57	0.000
Smoke (%)	22	23.2	0.454

Conclusions
In our series, MHO have a lower cardiovascular risk both for the scale and for Framinghan, adjusting for age, sex and degree of obesity.
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Menopausal hormone therapy is associated with reduced fat mass and in particular a significant decrease of the intravisceral abdominal fat, the OsteoLaus cohort

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Background
We previously showed that menopausal hormone therapy (MHT) favorably affects both bone density and microarchitecture with persistent benefit after its withdrawal (1). Looking for indirect factors contributing to bone effects, we investigated the relation between MHT and changes on fat and lean (muscular) tissue. Existing results on MHT and body composition are conflicting and large cohort studies are lacking.
Material and methods
The OsteoLaus cross-sectional population-based study includes 1'500 women aged 50 to 80 years (Lausanne, Switzerland). Current or past MHT use was assessed by questionnaire. Body composition evaluation by DXA was performed in a subgroup ($n=1094$). After exclusion of participants with hormone modifying treatments, the remaining women were divided in 3 groups based on MHT status: Never (NU, $n=549$), Current (CU, $n=216$) and Past (PU, $n=288$) Users.
Results
The 3 groups differed in age: 66.8±6.3, 62.6±6.7 and 61.3±7.9 years for PU, CU and NU respectively. Average time since MHT withdrawal in PU was 8.5 years. All the results were age-adjusted. CU exhibited lower BMI (−0.9 kg/m^2), compared to NU ($P=.02$). In particular, reduced intravisceral and android fat was noted (CU vs PU, $P=.02$ and .03 respectively). Total fat mass tended to be lower for CU ($P=.06$) with absolute values of 22.0±0.5 and 23.3±0.5 kg in CU and NU respectively. PU did not present any benefit regarding fat tissue in comparison with NU. That was the case even when only early MHT discontinuers (<2 years) were analyzed. There was no difference between groups regarding gynoid fat mass. Both CU and PU showed did not statistically exceed NU regarding total or regional lean mass nor muscle strength assessed by handgrip measurement. Assessment of caloric intake and physical activity did not reveal differences that could explain MHT-related fat mass reduction.
Conclusion
MHT is associated with less adiposity, due to reduction in android fat mass. The significant decrease of intravisceral fat mass in CU is of particular interest, given the strong link of the latter with cardiovascular risk. In contrast to our previous data for bone parameters, the benefit of MHT for fat mass reduction is not preserved in PU.
(1): Papadakis G. et al. The Benefit of Menopausal Hormone Therapy on Bone Density and Microarchitecture Persists After its Withdrawal. *J Clin Endocrinol Metab.* 2016 Dec; 101(12):5004-5011.
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Effect of surgical weight loss on the inflammatory hematological parameters in short term

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Introduction
In obesity, MPV is found higher compared to healthy controls. It was found that the level of NLR was predictive of the development of type 2 diabetes with high sensitivity and specificity in morbid obese patients. PLR is a new biological indicator that can assess the presence and severity of inflammation. However, in obese patients PLR was not found to associate with degree of of obesity or ratio of weight loss. Regarding the platelet count (PC) in obesity, conflicting results were reported. In some, although increased, the platelet counts were still in the normal range in obese patients.
Aim
In this study we aimed to observe the effect of surgical weight loss on Inflammatory hematological parameters and to observe the correlation between weight loss rate and hematological parameters.
Materials and methods
Eighty patients were included into the study and blood samples were taken at preop and at 3rd and 6th months.
Results
Decreases in NLR and MPV both 3rd and 6th months were statistically significant. PLR did not change at both 3rd and 6th months compared to baseline but PC was significantly lower at both 3rd and 6th months. Correlation analysis did not demonstrate any correlation between weight loss rate and MPV, NLR and PC but did with PLR at 3rd month however at 6th month there was no correlation between all the hematologic parameters and weight loss.

MPV	P
3. mo→0. mo	<0.001
6. mo→0. mo	0.008
NLR	P
3. mo→0. mo	<0.001
6. mo→0. mo	0.001
PLR	P
3. mo→0. mo	0.666
6. mo→0. mo	0.870
PC(10^3/ml)	P
3. mo→0. mo	<0.001
6. mo→0. mo	<0.001

Discussion
We studied preoperatively and postoperatively MPV, NLR, PLR, PLT changes in patients who underwent bariatric surgery. Post op values demostrated improvement in MPV, decrease in NLR, PLT at 3rd and 6th months, but we observed that these changes did not correlate with weight loss rates. These data are consistent with the literature and show that the inflammation formed by obesity regresses after surgery. The fact that the changes in these parameters are independent of the weight loss rates suggests that our data primarily represent early results and secondly it may be the effect of individual metabolic differences.

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Carotidintima-mediacomplexthickness and sex steroid levels in severly obese women of reproductive age

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Introduction
Obesity is often accompanied by comorbidites predisposing atherosclerosis. Carotid intima-media complex thickness (CIMT) is consisdered as a marker of initial asymptomatic atherosclerosis. The relationship of sex hormones to obesity and atherosclerosis has been extensively studied.
Objective
The objective of the study was to analyze the correlation CIMT and sex steroid levels in severly obese pre-menopausal women.
Methods and patients
This was a cross-sectional clinical study. The study included 65 severely obese pre-menopausal women aged 35.0±8.7 years with Body Mass Index (BMI) ≥35 kg/m^2. Anthropometric parameters and reproductive hormones were measured. Carotid intima-media thickness (CIMT) was assessed using a high-resolution B-mode ultrasound system. The average of maximal values of the right and left CIMT were used as a mean CIMT value.
Results
Anthropometric, hormonal and CIMT data was as follows: TT 124.1±24.0 kg, BMI 47.8±9.2 kg/m^2, waist circumference 127.6±17.9 cm, hip circumference 138.5±17.6 cm, FSH 8.1±3.4 IU/l, LH 4.8±2.9 IU/l, estradiol 196.4±109.0 pmol/l, testosterone 2.48±2.9 nmol/l, SHBG 23.1±12.0 nmol/l, androstendione 2.25±1.2 ng/ml, DHEAS 5.2±3.6 μmol/l, CIMT 0.44±0.1 mm. There was significant correlation between CIMT and waist circumference ($P<0.05$), without significant corelation between CMIT and sex steroid levels ($P>0.05$).
Conclusion
Obesity, especially central obesity has the crucial influence on carotid intima-media complex thickness and cardiovascular events in the future.

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Effect of pre-gestational weight and gestational weight gain in women with gestational diabetes controlled with medication on pregnancy outcome-is recommended weight gain too liberal?

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Aim
The aim of this study was to evaluate the effect of pre-gestational body mass index (BMI) and gestational weight gain (GWG) on adverse pregnancy outcomes in women with gestational diabetes mellitus (GDM) controlled with medication.
Methods
We conducted a retrospective cohort study of women with singleton pregnancies, diagnosed with GDM and treated with glucose lowering agents that were followed and gave birth between 2005–2015 in the Assaf Harofeh medical center, Israel.
Results
There were 280 women who met inclusion criteria. Mean maternal age was 33.92±5.2; 64.8% had a family history of DM and 39.7% had a history of GDM in previous pregnancies. Classification and regression tree method identified four groups according to adverse outcomes, consisted of 74 women with pre-gestational BMI below 25, 98 women with BMI 25–31, 90 women 31–39 and 18 women above 39. Respectively, the mean GWG was 12 kg (8–16), 11 kg (8–15), 7.5 kg (3.75–11) and 5 kg (-1.5–11.5). Mean GWG was significantly ($P<0.001$) different between groups. The risk for composite maternal and neonatal adverse outcomes was higher in the groups of BMI 25–31 (73.5%) and 31–39 (83.3%) in comparison to BMI <25 (51.4%) and 39< (55.6%), $P<0.001$. In the subgroup of women with pre-gestational BMI of <25, weight gain of more than the median resulted in odds ratio of 2.75 (1.07–7.08, p=0.036) for adverse pregnancy outcomes compared with women who gained less than the Mean GWG. When adjusted for potential confounders, the odds ratio for adverse outcome in women with BMI <25 who gained above the median weight increased to 4.8 (1.6–14.5, $P=<0.001$). Maternal age was independently associated with adverse outcomes in women with BMI 25–39 but not above 39, though this subgroup was relatively small.
Conclusion
Maternal obesity is related to adverse pregnancy outcomes. Moreover, GDM women with normal pre-gestational BMI who gained weight according to latest institute of medicine recommendations still experienced adverse outcomes. It is possible that weight gain recommendations for this group are too liberal.

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P560

The effects of endurance exercise training on chemerin, apelin, and visfatin in metabolically healthy obese young males

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Purpose
This study investigated the exercise-induced changes in novel adipokines (visfatin, chemerin, and apelin) related to obesity and metabolism, and their correlations with the changes in the measures of obesity and glucose homeostasis after the 8-wk exercise intervention.
Methods
Forty metabolically heathy obese young males were randomly assigned either to control (*C*, $n=12$) or exercise group (*Ex*, $n=28$). The subjects in exercise group participated in an 8-wk supervised endurance exercise training program and they

completed four sessions of treadmill running at 65-75% of their maximal oxygen consumption to burn approximately 600 Kcal per session. Anthropometric measures, various metabolic serum markers and the serum concentrations of total adiponectin, high molecular weighted adiponectin, leptin, visfatin, chemerin, and apelin were assessed at pre- and post-intervention.
Results
Serum levels of visfatin, chemerin, and apelin were significantly more decreased in *Ex* compare to *C* group during 8-wk intervention (-5.96 ± 6.07 vs. 0.75 ± 2.29 ng/mL, −26.64 ± 40.15 vs. 19.0 ± 43.61 ng/mL and −129.47 ± 138.01 vs. 83.08 ± 153.39 pg/mL, *respectively*, all $P < .05$). The change in serum apelin level was significantly correlated with the changes in fasting plasma insulin (FPI, $\beta = 0.672$), homeostasis model for insulin resistance (HOMA-IR, $\beta = 0.603$) and β-cell function (HOMA-β, $\beta = 0.696$), and quantitative insulin sensitivity check index (QUICKI, $\beta = -0.613$, *all* $P < 0.05$). These correlations remained after the adjustment for the confounders. The changes in visfatin and chemerin showed significant correlations with the changes in obesity measures.
Conclusions
Endurance exercise induced significant changes in serum concentrations of visfatin, chemerin and apelin in metabolically healthy obese young males. These changes seem to be involved in the etiology of obesity and glucose homeostasis

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P561

Absence of leptin signaling during development causes metabolic and neuronal disturbances in adult life

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The hormone leptin is required for the energy balance regulation. However, leptin also controls many other biological functions. Among these actions, some authors suggest that leptin exhibits neurotrophic effects in early life and plays a key role in the development of neurocircuitries that regulate energy metabolism. However, the precise role of leptin during development is still unclear. Thus, our study had the objective to investigate the consequences of the absence of leptin signaling during development. For this purpose, a LoxP-flanked transcription-blocking cassette was inserted in the *Lepr* gene to generate mice *Null* for the leptin receptor (LepR). This mouse was bred with animals expressing Cre-ERT2 fusion protein under the human ubiquitin C promoter sequence. Consequently, tamoxifen injections can induce Cre Recombinase activity and restore LepR gene expression in LepRNull-Ubi mice. Adult LepRNull and LepRNull-Ubi mice were morbidly obese and hyperphagic, as expected. LepR reactivation in 10 week old animals caused a robust decrease in food intake and body weight only in LepRNull-Ubi mice. While LepRNull mice remained unresponsive to leptin, an acute leptin injection was able to induce STAT3 phosphorylation in the hypothalamus of LepRNull-Ubi mice after tamoxifen treatment and reduce their food intake to a similar extent than control lean (Ubi) mice. Six weeks after LepR reactivation, food intake of LepRNull-Ubi mice was completely normalized. However, LepRNull-Ubi mice remained heavier and had higher body adiposity and leptinemia than Ubi mice, possibly due to a partial recovery in their energy expenditure. This defect is not explained by weight loss since LepR reactivation before the onset of obesity (4 weeks of life) could not prevent the suppressed energy expenditure of LepRNull-Ubi mice. In contrast, the insulin resistance exhibited by the reactivation of LepR in adult mice was no longer apparent when the reactivation occurred in younger LepRNull-Ubi mice, suggesting a weight loss-induced effect. Hypothalamic mRNA levels of AgRP and NPY were restored in LepRNull-Ubi mice, but POMC and CART expression remained suppressed. Notably, LepR reactivation in adult animals increased brain mass, but was not enough to normalize it. Conversely, the neural projections from the arcuate nucleus (ARH) to the paraventricular nucleus were completely restored in adult LepRNull-Ubi mice to levels found in lean control mice. In summary, we provided novel and substantial evidence that leptin signaling during early life is required for the energy homeostasis in adulthood, but not via the development of ARH neural projections.

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The relationship between arterial stiffness and obesity in kidney transplant recipients

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Obesity and cardiovascular disease (CVD) risk in recipients increase after kidney transplantation due to immunosuppressive drugs, non-traditional risk factors related to immunosuppressive drugs or chronic kidney disease (CKD). Inflammation, endothelial dysfunction, arterial stiffness (AS) and vascular calcification are common complications contributed to the development of CVD in patients with CKD. We aimed to evaluate the relationship between AS and obesity in transplant recipients.
Methods
This cross-sectional study conducted in consecutive 62 patients who underwent kidney transplantation. Our cohort excluded patients with coronary artery disease and heart failure. The patients were divided into three groups according to body mass index (BMI, kg/m^2): normal weight (<25, $n=28$, 8 males), overweight (25-29.9, $n=23$, 16 males) and obese (≥ 30, $n=11$, 5 males). Laboratory tests, high sensitive C-reactive protein (hsCRP), left ventricle mass index (LVMI), left ventricular hypertrophy (LVH) and AS (large vessel elasticity index-C1, small vessel elasticity index-C2) were measured.
Results
Median dialysis duration and follow-up time after transplant were 33 and 20 months, respectively. The mean age of overweight group was higher than that of normal weight group ($P < 0.026$). Donor age, blood pressures, dialysis and transplant durations, hypertensive and diabetic patient ratios, serum creatinine, uric acid, glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and urinary albumin excretion levels in the groups were comparable. Being smoker (27.3%, $P=0.020$) and family obesity history (63.6%, $P=0.002$) in obese group was higher than other groups. The CKD-EPI glomerular filtration rate in normal weight group (66.7 ± 17.7 ml/min) was higher than those of overweight (54.3 ± 19.7 ml/min, $P=0.017$) and obese (61.2 ± 19.5 ml/min, $P=0.047$) groups. The LVMI and hsCRP level in obese group was higher than that of normal weight (140 ± 28 vs. 117 ± 31 g/m^2, $P=0.003$ and 3.46 ± 6.2 vs. 11.9 ± 14.2 mg/l, $P=0.037$, respectively). There was no significant difference in proteinuria, anemia, LVH and valvular calcification ratios, C1 and C2 measurements between three groups.
Conclusion
We found that LVMI and hsCRP were higher in obese recipients, but not non-traditional risk factors such as anemia, proteinuria and AS.

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Anti-obesity effect of green alga sulphated polysaccharide on high fat diet

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Obesity is considered as an exceeding life style disorder notably in developing countries and it is prevailing at a frightful speed in new world countries as a result of fast food intake, causing raised blood cholesterol levels, which in turn can damage many systems in the body. The present study investigates the hypolipidemic effects of sulphated polysaccharide obtained from Codium fragile (CFSP) in induced obese rats (HFD). The results showed an increase in body weight of HFD rats by 21.56% as compared to control normal rats. Moreover, serum lipase activity underwent an increase which led to an increase in the levels of total cholesterol (T-Ch), triglycerides (TG) and low density lipoprotein cholesterol (LDL-Ch) in serum associeted with a decrease in the level of high density lipoprotein cholesterol (HDL-Ch) in untreated HFD rats. This diet has disrupted the antioxidant status by decreasing the activities of antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX)) and subsequently an increase in thiobarbituric acid reactive substances (TBARS) level in liver and kidney of obese rats. All these disturbances are significantly corrected by CFSP administration with no fatty deposits in the liver and a protective effect against renal histological alteration. This confirms the important role of this polysaccharide in the fight against oxidative stress and the prevention of hyperlipidemia.

Keywords: Green alga, Antioxidant, Hyperlipidemia, Liver-kidney functions.
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Serum oxytocin in elderly patients with metabolic syndrome

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Background
The term metabolic syndrome refers to a cluster of associated symptoms composed of impaired fasting glucose, abdominal obesity, hypertension, and dyslipidaemia. Metabolic syndrome is associated with an increased risk of cardiovascular and diabetes-associated morbidity and mortality. Further, there is evidence that metabolic syndrome is an effective and simple clinical tool for identifying high-risk subjects predisposed to cardiovascular diseases and diabetes mellitus type2. Oxytocin regulates food intake, carbohydrate and lipid metabolism. They respond to an increase in glucose and insulin (which occurs in metabolic syndrome as a powerful example for hyperinsulinemia due to insulin resistance and consequently hyperglycaemia) with an increase in intracellular [Ca2+] and increased oxytocin release.
Aim of the work
To assess the relationship between serum oxytocin levels and presence of metabolic syndrome in patients over 55 years old.
Patient and Methods
Our study was conducted on 90 elderly subjects (aged 55 years old or more). They were divided into Group I, 60 patients fulfilling the criteria of metabolic syndrome, according to guidelines from the National Heart, Lung, and Blood Institute (NHLBI), group II, 30 healthy subjects as a control group. All participants were subjected to history taking, full clinical examination, anthropometric measurement and laboratory investigations including Fasting plasma glucose, 2 hours plasma glucose, HbA1c, serum cholesterol, triglycerides, LDL-c, HDL-c, insulin resistance by HOMA, serum oxytocin.
Results
Serum oxytocin levels in patients with metabolic syndrome were significantly higher (Median = 25 (21–56.5)) than in control group (Median = 19.5 (16–23) with ($Z = -2.700$ and $P = 0.007$). Its level was significantly positively correlated with Waist circumference ($r = 0.336$, $P = 0.009$), DM duration ($r = 0.604$, $P = 0.000$), and FPG ($r = 0.411$, $P = 0.000$). It was found that the level of oxytocin in men was higher (IQR = 50(22–80) than in women (IQR = 22(20–25) with ($Z = -3.398$ $P = 0.001$).
Conclusion
Serum oxytocin is higher in elderly patients with metabolic syndrome with significant rise more observed in males than in females.

Keywords: Oxytocin, Elderly, Metabolic syndrome, Waist Circumference, Fasting plasma glucose.
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Study on some biochemical parameters in peripheral blood of animals upon diet-induced obesity and insulin resistance modeling

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The work was initiated to study some biochemical parameters in peripheral blood of animals upon diet-induced obesity and insulin resistance modeling. Obesity was induced in BALB/c mice by keeping them on the high- carbon diet for 13 weeks. The commercially available kits were used to assay glucose, alkaline phosphatase, creatine kinase and cholesterol; concentrations of testosterone were measured by the enzyme immunoassay. The high carbon diet in BALB/c mice served as a basis for the animal model with experimental obesity and insulin resistance. In the animals the diet-induced obesity was accompanied with body mass gain (by 48%), increase in the levels of glucose (6.68 ± 0.94 versus 2.43 ± 0.52 mmol/l in the control animals) and total cholesterol (2.02 ± 0.52 versus 0.54 ± 0.20 mmol/l in the control animals), and reduction in their insulin sensitivity. The high carbon diet used in the study was established to cause changes in blood serum biochemical parameters. The activities of alkaline phosphatase and creatine kinase were found to decline to be 64.9 ± 7.88 IU versus 347.6 ± 13.8 IU and 56.6 ± 2.11 U/l versus 364.0 ± 10.37 U/l in the controls, respectively. The changes could associate with injuries of hepatocytes due to type 2 diabetes mellitus onset. Concentrations of testosterone in the animals under study were found increased (66.05 nmol/l versus 34.33 ± 3.38 nmol/l in the controls), and obesity, lipid metabolism disorders and insulin resistance are thought to induce the increase of the hormone in the experimental animals' blood serum. All the changes above could be attributed to the compensatory mechanisms triggering restoration of functional and proliferative activity of hepatocytes. The 13-week high-carbon diet in BALB/c mice was shown to cause diet-induced obesity with insulin resistance accompanied by changes in some biochemical parameters of experimental animals' blood.

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P566

Does follicle stimulating hormone effect adiposity in patients with hypergonadotrophic hypogonadism: a retrospective study

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Introduction
Recent studies showed that post-menopausal osteoporosis and weight gain starts at the perimenopause stage, a period characterized by relatively stable estrogen and rising FSH levels. FSH is found to be associated with adiposity in women, which is also a great risk factor for type 2 DM. There is also a sharp increase in visceral adiposity during this life stage, which coincides with the emergence of disrupted energy balance and reduced physical activity. There is consistent evidence from basic and preclinical research that the disruption of estradiol signaling, accelerates fat accumulation. The excess fat seems to accumulate disproportionately in the abdominal region and leads to insulin resistance and dyslipidemia. We therefore decided to investigate the FSH – BMI and waist circumference relation in a small group of male patient with hyper gonadotrophic hypogonadism, who have similar laboratuary values of perimenopausal women.
Methods
A total of 230 young male patients with newly diagnosed hyper gonadotrophic hypogonadism (mean age: 21.16 ± 1.79 years) were analyzed retrospectively. 77 of the patients had a diagnose of Klinefelter's syndrome, the rest didn't have any genetic testing. Only the measurements at the time of diagnosis (untreated) were taken. FSH, LH, total and free testosterone, estradiol were analyzed for possible correlation with BMI and waist circumference.
Results
The mean values of FSH, LH and total testosterone were all compatible with the diagnosis of hypergonadothrophic hypogonadism (Table 1). Only a slight negative correlation was found between LH and BMI. When we limited the analysis to the patients with documented diagnosis of Klinefelter's syndrome the results were similar.
Conclusion
We didn't find any significant correlation between FSH and abdominal circumference, waist circumference or BMI. The younger age and low BMI values of our study population may play role on these results. The lack of body fat

distribution analysis, either by bio-impedance or radiologic imaging techniques was also a limitation of our study.

Table 1 The demographic and metabolic parameters of the patients with hypergonadotrophic hypogonadism

	Patients (n = 230)
Age (yr)	21.16 (±1.79)
Diag. of KS (n,%)	77 (33.5%)
BMI (kg/m$^{2)}$	22.35 (±4.03)
AC (cm)	60.06 (±35.61)
WC (cm)	71.02 (±39.51)
Total-C (mg/dl)	163.46 (±30.42)
FSH (mIU/ml)	347.64 (±33.66)
LH (mIU/ml)	27.21 (±14.85)
T.Testosterone (ng/dl)	0.93 (±0.93)
F.Testosterone (μU/ml)	8.31 (±13.56)
Estradiol (pg/mL)	22.48 (±18.67)

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P567

Psychosocial aspects and hygiene-dietetic habits in a group of patients in follow-up before bariatric surgery

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Objectives
To evaluate the psychosocial aspects and the common dietary habits in a group of patients in follow-up in specific consultation of bariatric surgery prior to the intervention.
Methods
Cross-sectional study of patients in follow-up in the specific morbid obesity consultation of the University Hospital Puerta del Mar (Cádiz) not intervened.
Results
110 patients were analyzed, of which 68.2% are women, with an average age of 44.63 years. Regarding the level of studies, 30.2% had only primary studies and 47.7% had primary and secondary studies. 32.7% were unemployed and 8.4% were disabled. 55.5% acknowledge regular physical exercise and 56.1% recognize a fast food intake, although 83.6% refer to a healthy and balanced diet. The majority (83.7%) have good family support.
Conclusions
The profile of patients undergoing follow-up in our consultation prior to bariatric surgery usually presents a basic level of studies -primary and secondary-, relatively frequent in the case of unemployment or early retirement. Only half of patients exercise regularly and bad dietary habits persist in terms of fast food intake.

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P568

Psychosocial aspects and hygiene-dietetic habits in a group of patients intervened for bariatric surgery

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Objectives
To evaluate the psychosocial aspects and the common dietary habits in a group of patients undergoing bariatric surgery.
Methods
Cross-sectional study of patients in follow-up in the specific consultation of morbid obesity of the University Hospital Puerta del Mar (Cádiz) intervened, at 6–12 months of follow-up.
Results
88 patients were analyzed, of which 70.5% ($N = 62$) are women, with an average age of 45.01 ± 8.55 years. The BMI before the intervention was 47.29 ± 5.54 kg/m^2 being 34.52 ± 6.48 kg/m^2 at present. Regarding the level of studies, 30.2% had only primary studies. 26.7% were unemployed and 15% disabled. 81.6% admit regular physical exercise and 12.9% admit fast food intake after surgery, and 20.7% continue with snacking throughout the day. The majority (90.7%) has good family support.
Conclusions
The profile of the patients in our area usually presents a basic level of studies -primary and secondary-, in situations of unemployment or early retirement, and after surgery they show changes in their dietary habits and physical exercise, although they frequently persist with inadequate habits.

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P569

Body mass index versus visceral adiposity index as predictors for dyslipidemia and liver stiffness in HIV/HCV co-infected patients with liver fibrosis

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Introduction
Association between liver fibrosis and body mass index (BMI) is well known in HIV/HCV patients, is linked to worse lipid profile and is widely used to predict liver fibrosis in this population. Nevertheless, recent studies show a stronger link between dyslipidemia and liver stiffness with visceral adiposity index (VAI) in general population. The main aim of this study was to investigate the accuracy of VAI and BMI as predictors for liver fibrosis and dyslipidemia in a cohort of HIV/HCV co-infected patients.
Methods/design
We conducted a cross-sectional study in a cohort of HIV/HCV co-infected outpatients attended in our hospital. Demographic, clinical and anthropometric variables were collected. Liver stiffness was measured by transient elastography (Fibroscan™). Liver fibrosis was defined as the presence of a liver stiffness ≥ 7.2 kPa. Patients were classified as obese, if BMI ≥ 30 kg/m^2, and as normal weight if BMI between 18.5 – 24.9 kg/m^2. Further, patients were divided into three groups according to VAI score tertiles.
Results
Thirty-nine HIV/HCV co-infected individuals (97.4% male, mean age: 47.4 ± 5.2 years) were included. Patients with normal weight compared to obese individuals had significantly lower HDLc levels (41.4 ± 8.8 mg/dl vs 51.4 ± 16.7 mg/dl; $P = 0.03$) but no differences were found in other lipid profile, in a univariate analysis. When the cohort was classified according to VAI tertiles, patients with the highest VAI score (third tertile) had higher triglycerides serum levels (233.1 ± 81.2 vs 85.9 ± 31.1 mg/dl; $P < 0.001$), higher LDLc levels (115.1 ± 40.1 vs 78 ± 22.2 mg/dl; $P = 0.006$) and lower HDLc (34.4 ± 8.2 vs 60.9 ± 16.7 mg/dl; $P < 0.001$). Though both BMI and VAI showed a positive correlation with liver stiffness, this association was stronger for VAI than the observed for BMI ($r = 0.392$; $P = 0.004$ vs $r = 0.291$; $P = 0.035$).
Conclusions
According to our results, VAI score is more accurate than BMI to predict liver fibrosis and dyslipidemia in this population. We propose routine use of VAI to identify HIV/HCV co-infected patients at risk for liver fibrosis and/or dyslipidemia.

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P570

Abstract withdrawn.

P571

Effect of 8 weeks of hypocaloric diet and physical activity on thyroid hormones, irisin and insulin sensitivity in obese otherwise healthy subjects.

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Hypothyroidism is associated with modest weight gain, but there is a lack of clarity regarding subclinical hypothyroidism and obesity. Studies with bariatric surgery showed that 15–25% of extremely obese subjects had subclinical hypothyroidism. Therefore the goal of this *study* was to evaluate the effect of intensified life style intervention on insulin sensitivity, irisin concentration and thyroid function parameters.

Methods

A randomized interventional clinical study (NCT02325804) included life style intervention: hypocaloric diet (30% restriction of calories) and physical activity 150 minutes/week. Before and after 8 weeks of intervention all patients underwent complete medical examination (measurement of physical fitness, resting metabolic rate (RMR), body composition analysis, oral glucose tolerance test, parameters of lipid metabolism, irisin concentration and thyroid function parameters. Insulin sensitivity was evaluated according to the homeostasis model assessment of insulin resistance (HOMA-IR) and insulin sensitivity indices according Matsuda and Cederholm were calculated (ISIMat and ISICed).

Results

So far 43 patients (14 M/29 F, mean age 43 ± 12 yrs., body fat % 36 ± 6) finished the intervention. At baseline 9 patients had thyroid stimulating hormone (TSH) in the range 2.5–5.0 ng/ml, indicating subclinical hypothyroidism. The average reduction of body weight was 6.8 ± 4.9 kg (0–15 kg; $P \leq 0.0001$), Insulin sensitivity improved (IR HOMA 2.71 ± 3.90 vs. 1.24 ± 0.83; $P = 0.01$; ISIMat 6.64 ± 4.38 vs. 8.93 ± 5.36 $P \leq 0.001$; ISICed 59.1 ± 21.4 vs. 64.7 ± 22.2 $P = 0.03$). TSH significantly decreased after intervention (2.04 ± 1.24 vs. 1.69 ± 0.81 $P = 0.03$) and free thyroxine remained unchanged (13.7 ± 2.7 vs. 13.4 ± 2.9, $P = 0.7$). Plasma irisin significantly decreased after intervention (233 ± 66 vs. 167 ± 88 ng/ml; $P \leq 0.001$) and positively correlated with ISImat, however only after intervention (P 0.05).

Conclusion

Results of our study are in line of previous results about beneficial effect of intensive life style changes on insulin sensitivity and thyroid function. Novel view indicates that changes in thyroid-stimulating hormone (TSH) could well be secondary to obesity. Supported by grants APVV 15-0228; VEGA 2/0161/16

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P572

The comparison of different obesity criterias in kidney transplant recipients

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Weight gain and obesity are frequent problems after kidney transplantation. Potential causes of weight gain are use of immunosuppressive drugs and changes in life style such as dietary intake and insufficient physical activity. This study aimed to evaluate the different general and abdominal obesity criterias and post-transplant weight changes in kidney transplant recipients.

Methods

This prospective study included consecutive 112 (62 females, 50 males) patients, with a mean age of 41.5 ± 11.1 years who underwent kidney transplantation. Obesity was assessed by calculating body mass index (BMI) for general obesity, and waist (WaC) and hip (HC) circumferences and waist to hip ratio (WHR) for abdominal obesity. Optimal WaC is evaluated and categorized differently by different organizations like International Diabetes Federation (IDF) and World Health Organization (WHO). Obesity classification according to WaC defined by IDF and WHO was ≥ 94 and ≥ 102 cm for males and ≥ 80 and ≥ 88 cm for females, respectively. WHR was considered as obese if > 0.9 for males and > 0.8 for females.

Results

The measurements of the patients were obtained during 4 years after transplantation. The median weight gain was 3.6 kg at 1st year ($n = 112$), 5.6 kg at 2nd year ($n = 112$), 7.8 kg at 3rd year ($n = 112$) and 8.5 kg at 4th year ($n = 95$, 43 males, 52 females). The median values at pre-transplant and post-transplant 1st, 2nd, 3rd and 4th years were 23.4, 25.0, 25.8, 25.8 and 26.5 kg/m^2 for BMI; 84, 89, 89, 90 and 90 cm for WaC; 94, 98, 98.5, 100 and 100 cm for HC; 0.9, 0.89, 0.89, 0.92 and 0.91 for WHR, respectively. The increases in these parameters were significant when compared to pretransplant values except WHR ($P < 0.001$). When the obesity criterias were evaluated separately, obese ratios for BMI, WaC-IDF, WaC-WHO and WHR were 7.1%, 42.9%, 20.5% and 75.9% at pre-transplant, 14.3%, 56.3%, 38.4% and 75.9% at 1st year, 20.5%, 55.4%, 41.1% and 69.6% at 2nd year, 24.1%, 58%, 40.2% and 68.8% at 3rd year, and 27.4%, 56.8%, 45.3% and 70.5% at 4th year, respectively.

Conclusion

We observed a continous weight gain in our kidney transplant patients. When different obesity criterias were taken into account, the ratios of obese patients also varied. The ratios were higher by WHR and lower by BMI. After the second year there was a relative slowdown at the rate of obesity increase. Abdominal obesity seemed to be a more prominent problem compared to general obesity.

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P573

Effect of the rs12324955 polymorphism of the FTO gene in the intervention for the weight reduction in obese patients with the use of technological resources

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Introduction

Obesity is a multifactorial disease in whose genetic factors are involved. The integration of this factors will allow to state personalized prevention strategies, where the constant contact with the patient will have a greater success for them to follow up recommendations. Continuous technological changes allow bigger accessibility to communication, having platforms with remote control.

Objective

Assessing the effectiveness of an Intelligent Platform of Biomedical to Monitor, Treat and Personalized Prevention in obesity and cardiometabolic risk versus a non technological intervention for the obesity treatment, considering the participants' genetic characteristics.

Materials and methods

71 obese subjects, between 18 and 65 years, of the PREDIRCAM study (prospective cohortes intervention study) were included. Recruitment, the participants were randomized in intensified intervention group (control group) or technological intensified intervention group (intervention group). The follow up was made for 6 months. Anthropometric data, biochemical data and environmental data with questionnaires were obtained. The rs12324955 of the FTO gene was determined through TaqMan probes.

Results

88.7% were women. After 6 months, data of 46.5% to the sample were obtained, because the rest had not completed the full term yet. After 6 months of intervention the subjects showed less weight, hip and BMI (weight: -4.39 ± 5.61 kg; hip: -3.93 ± 5.11 cm; BMI: -1.63 ± 1.96 kg/m^2, $P < 0{,}001$ in all cases) . When dividing according to the intervention group, technological group subjects showed also a significant reduction in the total and c-LDL according to the baseline (total cholesterol: -15.47 ± 21.01 mg/dl, $P = 0.008$; c-LDL: -10.19 ± 14.77 mg/dl $P = 0.015$). According to the genotype rs12324955 no differences were found in at baseline, but after intervention the carriers of the A allele showed a light greater decrease in weight that GG homozygotes (A carriers: -5.88 ± 5.00 kg, $P < 0.001$; GG homozygotes: -3.96 ± 2.95 kg, $P = 0.002$). After segmenting by the intervention group, everybody lost weight significantly after intervention, these differences were more significant in carriers of the A allele of the technological group (non technological: carriers A: -6.07 ± 6.41 kg $P = 0.022$, GG homozygotes: -4.50 ± 4.78 kg $P = 0.047$; technological: carriers A: -5.66 ± 3.16 kg $P = 0.001$, GG homozygotes:- 3.49 ± 3.33 kg $P = 0.021$).

Conclusion

The intensive intervention to modify the obese people's lifestyle shows a decrease in weight loss, being this intervention more effective in rs12324955 carriers A subjects and with intervention done using technological applications.

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P574

Novel indicator of abdominal obesity strongly associated with cardiovascular disease

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Obesity is one of the leading causes of elevated cardiovascular disease (CVD) mortality and morbidity. Several indicators of abdominal obesity such as body mass index (BMI) and waist circumference (WC) are available. BMI and WC have limitations in stratifying cardio-metabolic risks. Another obesity measure, A Body Shape Index (ABSI), has been introduced but its applicability remains limited. To address this, the z-score of the log-transformed ABSI (LBSIZ) was recently developed. This study aimed to examine the ability of LBSIZ, compared to that of WC and BMI, to predict CVD risk. The study included participants who were recruited from the Korean Genome and Epidemiology Study, a population-based cohort study and followed for 10 years. A total of 8485 participants were analysed. The area under the curve was 0.633 (95% confidence interval [CI]: 0.611-0.655) for LBSIZ, 0.604 (95% CI: 0.580-0.627) for WC, and 0.538 (95% CI: 0.514-0.562) for BMI. In multivariate Cox regression analysis, BMI and WC showed the lowest risk for CVD events in 2nd decile and an overall J-shaped relationship with their deciles (p-trend: <0.001 WC vs 0.03 BMI). However, LBSIZ showed the lowest risk for CVD events in the 1st decile and a linear relationship across its deciles (p-trend of <0.001). The results of this study indicate that participants with high level of LBSIZ have significantly higher rate of CVD events than those with low level and LBSIZ is more strongly associated with CVD risk than BMI and WC in general population.

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P575

The effect of laparoscopic sleeve gastrectomy on kidney function

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Introduction
Higher body mass index (BMI) has been associated with adverse renal outcomes, including chronic kidney disease (CKD), progression to end-stage renal disease (ESRD), nephrolithiasis and renal cell cancer. Several studies have shown that weight loss following bariatric surgery has a positive effect on kidney function, mediated by a reduction in proteinuria, glomerular hyperfiltration and improvements in blood pressure and insulin resistance. The aim of this study was to examine the changes in estimated glomerular filtration rate (eGFR) in a group of morbidly obese patients 6 months after laparoscopic sleeve gastrectomy (LSG).
Materials and methods
221 severely obese patients (65.2% women, mean age $=41.97\pm11.24$ years, mean BMI $=44.7\pm8.57$ kg/m^2) underwent a complete clinical and biochemical assessment before and 6 months after LSG. The variation of parameter values(Δ) was expressed in percentages out of the preoperative values. Kidney function was calculated using the MDRD-4 formula.
Results
Of the 221 patients, 53.4% were hypertensive, 25.4% had diabetes and 53.8% presented with metabolic syndrome (MetS). Six months after surgery BMI declined to 31.84 ± 6.7kg/m^2 ($P<0.001$) and an excess weight loss (EWL) of 73.86 ± 30.33% was observed. In addition, the prevalence of CKD risk factors decreased significantly to 34.3%, 8.5% and 14% for hypertension, diabetes and MetS respectively ($P<0.001$). Regarding the kindney function, 71.5% of patients had an eGFR lower than 90 ml/min/1.73 m^2, with mean eGFR $=82.15\pm18.50$ ml/min/1.73 m^2. Postoperatively, eGFR increased to 86.33 ± 20.4 ml/min/1.73 m^2 ($P<0.001$) and 60.2% had an eGFR <90 ml/min/1.73 m^2 ($P<0.001$). Negative correlations were established between ΔeGFR and ΔBMI ($r=-0.195$, $P=0.004$), Δcalcium levels ($r=-0.273$, $P=0.038$). Patients were further examined after being separated by baseline eGFR (<90 and >90 ml/min/1.73 m^2). Comparing the two groups, the patients from the eGFR <90 group were older (44.03 ± 10.09 vs 36.81 ± 10.2 years, $P<0.001$) and had a lower BMI (43.69 ± 7.97 vs 46.8 ± 9.6 kg/m^2, $P=0.014$). While a slight increase in eGFR was noticed in the <90 group (73.29 ± 10.38 preoperatively vs 79.28 ± 15.87 ml/min/1.73 m^2 postoperatively, $P<0.001$), there was no change in the >90 group (104.38 ± 15.48 preoperatively vs 104.02 ± 20.13 ml/min/1.73 m^2 postoperatively, $P=0.068$).
Conclusion
Bariatric surgery is an effective method of improving CKD risk factors such as hypertension and diabetes and weight loss is associated with an increase in eGFR in patients with renal impairment.

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P576

Prevalence and pathophysiology of early dumping in patients after primary Roux-en-Y gastric bypass during a mixed meal tolerance test

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Introduction
The endocrinologist is confronted with an increasingly large population of postbariatric patients who present with endocrine problems. One of these is early dumping, a complication that may be the result of increased entero-endocrine activity. To address the prevalence of early dumping and to gain further insight into its pathophysiology, we performed a Mixed Meal Tolerance Test (MMTT) in a random sample of patients after Roux-en-Y gastric bypass (RYGB).
Methods
A random sample of 140 patients who underwent primary RYGB surgery between 2008 and 2011 were invited to participate. In total, 46 patients completed the MMTT with a standardized liquid supplement. The Dumping Severity Score (DSS) for early dumping was assessed every 30 minutes. Blood samples were collected at baseline, every 10 min during the first half hour and at 60 min after the start. The samples were assessed for hematocrit and glucagon-like-peptide-1 (GLP-1), Peptide YY (PYY), and vasoactive intestinal peptide (VIP).
Results
The prevalence of a high suspicion of early dumping based on the DSS was 26%. There was no difference in blood pressure and heart rate between patients with high or low suspicion of early dumping. The percentual change in hematocrit was slightly higher in patients with high suspicion of early dumping. No differences were seen for inactive GLP-1 and VIP between patients with high or low suspicion of early dumping. Patients with high suspicion of early dumping had higher levels of active GLP-1 and PYY.
Conclusion
The prevalence of complaints suggestive of early dumping in a random population of patients at mid-term post-RYGB is 26 percent in response to a mixed meal. Postprandial increases in both GLP-1 and PYY are associated with complaints of early dumping, suggesting gut L-cell overactivity in this syndrome.

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P577

Weight loss and metabolic parameters after laparoscopic sleeve gastrectomy

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Introduction
Obesity, defined as a BMI ≥30 kg/m^2, is the most common chronic metabolic disease in the world and its prevalence has strongly increased. *Obesity* is associated with multiple comorbidities, including cardiovascular disease, hypertension, insulin resistance, dyslipidemia, type 2 diabetes, sleep apnea and

certain cancers. Bariatric surgery is the most effective treatment for severe obesity and produces dramatic and durable weight loss. The aim of the study was to evaluate weight loss and changes in the metabolic profile in a period between 6 months and 5 years after laparoscopic sleeve gastrectomy (LSG).
Methods
An observational study was conducted. It included 40 patients having morbid obesity and undergoing bariatric surgery, respectively LSG. Preoperative and postoperative data (6 months and 5 years) was collected and analyzed. The following parameters were measured: weight, height, waist, hip; BMI and EWL (excess weight loss) were calculated. Fasting glucose, insulin level, uric acid and lipid profile were measured and HOMA IR (homeostasis model assessment of insulin resistance) was calculated.
Results
Preoperatively, the mean age was 44.55 ± 8.95 years, mean BMI was 46.61 ± 10.06 kg/m^2, mean waist was 131.25 ± 20.30 cm, and mean cholesterol level was 210 ± 41.47 mg/dl. After 6 months, mean BMI decreased to 33.95 ± 7.28 kg/m^2 and to 35.11 ± 7.28 kg/m^2 after 5 years. On average, patients had EWL of 66.71% at 6-month follow-up and 57.29% at 5-years follow-up. There were remarkable improvements in lipid profile. The mean levels of high-density lipoprotein (HDL) cholesterol after surgery were significantly higher (41.95 ± 9.53 mg/dl vs 47.42 ± 12.09 mg/dl six months after surgery vs 54.25 ± 12.52 mg/dl after 5 years, $P < 0.05$). Triglycerides, uric acid and glucose levels were significantly reduced from 159.69 ± 66.644 mg/dl, 7.39 ± 4.81 mg/dl and 118.64 mg/dl at baseline to 108.23 ± 79 mg/dl, 5.07 ± 1.55 mg/dl, and 86.08 ± 9.72 mg/dl after 6 months and 105.24 ± 51.86 mg/dl, 5.49 ± 1.25 mg/dl, and 93.96 ± 13.73 mg/dl after 5 years. After 6 months, HOMA index improved from 7.62 ± 7.25 to 1.44 ± 1.59 ($P < 0.05$). Compared to baseline, improvement was maintained in the data collected after 5 years (2.97 ± 3.58, $P < 0.05$).
Conclusion
LGS determines both short and long term improvements in weight loss and metabolic parameters.

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P578

Anthropometric and body composition evolution in individuals in weight loss

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Introduction
A large proportion of the Portuguese population has overweight and the process of weight loss is often focused solely on weight. However, it is essential that there is a good evolution of the body composition, namely in the decrease of fat.
Objective
Evaluate the anthropometric and body composition evolution in a group of individuals followed for a weight loss.
Methodology
This sample consisted of 30 adult and who were being followed up at a weight loss clinic. An initial anthropometric evaluation (M0) was performed by weight (kg) and height (cm) and body mass index (kg/m^2) was calculated. Body composition was assessed using a tetrapolar bioimpedance (Bodystat 1500) and it was prescribed a structured individual food plan. The body composition evaluation included fat (%), fat mass (kg), fat free mass (%) and total body water (%). The same evaluations were performed after 1 month (M1) and 2 months (M2).
Results
This sample consisted of 70% ($n = 21$) of female subjects and had a mean age of 40 (± 12.9) years. The percentage of the mean weight lost to M1 was 3.44 (± 3.38)% and up to the M2 of 5.53 (± 3.13)%. The mean body fat percentage lost to M1 was 3.69 (± 5.86)% and up to M2 of 6.93 (± 5.50)%. Women lost a higher percentage of weight, but men lost a higher percentage of fat. Weight and fat loss were always higher in the first month in both sexes.
Conclusions
Despite the evolution of weight loss, it is in the decrease of body fat that there is a greater evolution, and it is in the first month that the positive evolution in these parameters was more pronounced.

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P579

Free and dipeptide forms of L-glutamine supplementation attenuate parameters of oxidative stress and nonalcoholic fatty liver disease (NAFLD), and improve glucose metabolism in insulin resistant Ob/Ob mice

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Introduction
The availability of the body's most abundant amino acid, glutamine is compromised in obesity-associated diabetes. This may impair glucose metabolism by increasing hepatic insulin resistance, oxidative stress and the development of nonalcoholic fatty liver disease (NAFLD).
Objective
Evaluate the effects of free and dipeptide (DIP, L-alanyl-L-glutamine) forms of L-glutamine on glucose metabolism, biomarkers of oxidative stress and NAFLD in insulin resistant Ob/Ob mice.
Methods
C57/BL6 adult male mice were distributed into five groups: WT and Ob/Ob (CTRL) mice receiving water, and Ob/Ob mice supplemented with either DIP or free L-glutamine (GLN). The supplements were offered in a 4% drinking water solution for 40 days prior to euthanasia. Glucose metabolism was evaluated by glucose and insulin tolerance tests (GTT and ITT, respectively) performed at the end of the 40 days of supplementation. After euthanasia plasma glutamine, glucose, insulin and triglycerides (TG) concentrations were analysed. TG, reduced and oxidized glutathione (GSH and GSSG, respectively), TBARS, translocation of NRF-2, and histology were measured in the liver. Statistical differences between groups were determined using One-way ANOVA with post-hoc Tukey HSD.
Results
In plasma, GLN and DIP supplements increased glutamine concentration, while fasting TG, glucose and insulin levels reduced compared to the CTRL group ($P < 0.05$). GLN and DIP supplements also improved GTT and ITT responses. This result could be linked to an observed increase in glutamine and GSH concentration, NRF-2 translocation, as well as reduced TG and fat droplets deposition in the liver ($P < 0.05$).
Conclusion
Free and DIP forms of L-glutamine supplementation attenuate parameters of oxidative stress and NAFLD, and improve glucose metabolism in insulin resistant Ob/Ob mice.

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P580

Role of IGF1 in regulation of SOD 1 expression and mTOR/S6K signaling in heart of obese male rats

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Aim
Obesity is associated with activation of mammalian target of rapamycin (mTOR)/ribosomal S6 kinase (S6K) signaling pathway that promotes cardiac hypertrophy, insulin resistance, endothelial dysfunction and oxidative stress. Although activation of mTOR/S6K has a harmful effect, simultaneously it represents adaptive metabolic response that protects cells from excessive nutrient intake. Insulin like growth factor-1 (IGF1) exerts pleiotropic action on heart promoting vasorelaxation, antiinflammatory, antiatherogenic and antioxidant activity. Aim of this study was to evaluate how IGF1 treatment influences mTOR/S6K signaling pathway and SOD 1 expression in heart of obese rats.
Methods
Male Wistar rats were fed with standard laboratory diet or high fat (HF) diet (42% of fat) for 12 weeks and then half of all animals were treated intraperitoneally with one dose of IGF1 (50 μg/kg). After 24 h of treatment the animals were sacrificed and hearts excised. The expression of SOD 1 protein and phosphorylation and expression of mTOR and p70 S6K proteins were measured in rat heart lysates by Western blot method.

Results
Decreased level of SOD1 protein was observed in hearts of normally fed rats treated with IGF1 ($P<0.01$) and obese rats ($P<0.001$), while it was increased in IGF1 treated obese rats. The activation of cardiac mTOR was increased in normally fed IGF1 treated rats ($P<0.001$) and obese rats ($P<0.05$), while it was decreased in IGF1 treated obese rats ($P<0.01$). The results also show that activation of p70 S6K was increased in heart of normally fed rats treated with IGF1 ($P<0.01$) and obese rats ($P<0.05$), while it was decreased in IGF1 treated obese rats ($P<0.05$).
Conclusion
Results suggest that in heart of obese rats, IGF1 mitigates detrimental effects of obesity by increasing expression of SOD 1 protein, probably through mechanism that involves downregulation of mTOR/p70 S6K signaling pathway.

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P581

Plasma metabolomic markers of insulin resistance in humans.

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Introduction
Insulin resistance (IR), a pathological state of low sensitivity to insulin in humans and animlas, is closely associated with type 2 diabetes mellitus, obesity and cardiovasculare dieseas. IR can be quantified using detailed protocols, such as the euglycemic-hyperinsulinemic clamp (EC) technique and the intravenous glucose tolerance test, or based on indices derived from the oral glucose tolerance test. Although these indices showed greater association with the incidence of diabetes, they allow no personalized estimation of the individual risk and cannot be used for monitoring of the individual changes in the insulin resistance. The modification of nutritional pattern is one of the first steps of prevention the IR and associated diseases. Diets with increased intake of branched chain amino acid lead to increase in IR in animals and human, possibly via disruption of insulin signaling in skeletal muscle. Here we aimed to investigate the changes in the plasma metabolome during constant insulin infusion. Additionally, the correlations between baseline concentrations of metabolites and changes of IR, which was measured in the EC-experiments, after high-protein and control diet were studied.
Methods
In the first study (NCT00774488), middle-aged healthy obese subjects ($n=14$) underwent saline infusion and/or EC at a steady-state capillary plasma glucose concentration of 4.4 mmol/l. Plasma metabolites were measured using time-of-flight gas chromatography-mass spectrometry (GC-TOF/MS) technique. In the second study (NCT00579657), a randomized, controlled nutritional intervention (18-weeks) was conducted in 72 non-diabetic participants (overweight/obese: 29/43) with at least one further risk factor of metabolic syndrome. Participants were group-matched and allocated to 4 isoenergetic supplemented diets: control; high cereal-fiber; high-protein; or moderately increased cereal-fiber and protein (MIX). Whole-body IR was measured using EC. Plasma metabolome and IR were studied at 0, 6 and 18-weeks.
Results
Eight metabolites: altrose, asparagine, glycerol-2-phosphate, gulose, heptadecanoic acid, phenylalanine, pyroglutamate and talose correlated with high-protein diet-induced changes in IR and significantly changed during EC.
Conclusions
Multimarker strategy with use of plasma metabolic profiling appears to be a useful tool for both the assessment of IR and the 'metabolic signature of insulin effects' (i.e. doping control of elite athletes) in humans.

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P582

"A new life in a new body": the evolution of pregnancy following bariatric surgery in obese females

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Introduction
Maternal obesity (MO) increases the risk of gestational and neonatal complications. Bariatric surgery (BS) is currently the most effective long-term treatment of MO. The sustained weight loss after BS reduces the risk of maternal comorbidities during pregnancy. Nevertheless, BS is associated with an important risk of nutrients deficiency, and some data indicate that might increase the risk of prematurity and low birth weight. The objective of the present study is to evaluate the evolution of the pregnancy ending with a living child following bariatric surgery in obese females following BS in our center.
Methods
We performed a retrospective observational study by reviewing the medical records of MO females that underwent BS between January 2004 and October 2016 in our center and that had a pregnancy that finalized with a living child.
Results
A total of 20 pregnancies that finalized with a living child were registered. All the pregnancies were spontaneous, after 3.4 ± 2.9 years following BS. The BMI pre-BS was 43.9 ± 4.7 kg/m^2. At the moment of conception the maternal mean age was 33 ± 4.6 years and the BMI was 30.6 ± 4.9 kg/m^2. The course of gestation was normal and full term in all cases. Of all the patients, 8 (40%) underwent Sleeve gastrectomy (SG) and 12 (60%) underwent Roux-en-Y gastric bypass (RYGB). Gestacional diabetes was registered in 3 (15%) cases, similar to the general population. The birth weight of the children was 3032 ± 3.81 g. The incidence rate of small-for-gestational age birth was 25%, higher than 10% in the general population. There were no significant differences between the two surgical techniques regarding the evolution of pregnancy and the need of vitamin supplements. No neonatal complications were observed.
Conclusion
In our study BS did not increased the risk of prematurity or complications during pregnancy. We found an increased risk of small-for-gestational-age compared with general population.

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P583

Temporal analysis of the HFD consumption in the mice small intestine physiology: possible correlation between metabolic disorders and HFD-induced obesity

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Introduction and aim
Obesity is a public health problem characterized by metabolic and endocrine disorders. Currently, it has been observed an increase of the obesity induced by high fat diet (HFD) and, considering that small intestine is the most important absorptive site of the nutrients, it is very interesting to evaluate the impact of HFD intake on that first place of nutrients entry, that is, the small intestine. Taken into account that dyslipidemia and hypertension are obesity common findings, we attempted to evaluate whether HFD consumption affects the microsomal triglyceride transfer protein (MTTP) and NHE3, since they promote triglyceride and sodium absorption, respectively. Considering that nutrients absorption could contribute to body weight gain and obesity, we also evaluated the nutrients

transporters: SGLT1, GLUT2 and GLUT5 for carbohydrates, PEPT1 for peptides, FATP4, CD36/SR-B2 and NPC1L1 for long-chain fatty acids and cholesterol, respectively.
Methods
C57bl/6 male mice were fed standard diet (LFD) or HFD for three, six, nine or twelve weeks. At the end of each time, mice were killed and small intestine was removed and opened to detach the absorptive epithelium from mucosa. The epithelium was homogenate in appropriate lysis buffer and submitted to Western blotting (WB) technique for MTTP, NHE3, SGLT1, GLUT2, GLUT5, PEPT1, FATP4, CD36/SR-B2 and NPC1L1. PKA and PKC activities were analyzed by ELISA.
Results
HFD consumption from third up to 12th week increased MTTP and NHE3 content, but decreased the GLUT2, PEPT1 and NPC1L1. HFD also decreased the CD36/SR-B2 content, but only from 9th up to 12th week. HFD did not affect the SGLT1, GLUT5 and FATP4 content at any time-course studied. HFD also decreased PKA and PKC activities at 12th week.
Conclusion
Considering that mice began to gain weight from the third week after HFD consumption, the reduction of GLUT2, PEPT1 and NPC1L1 might interpose to the nutrients uptake, which could constitute a counter-regulation mechanism to limit the gain weight and adiposity. That condition could be reinforced by the decreased CD36/SR-B2 content observed from ninth week of HFD. Regarding the increase of MTTP and NHE3, we could infer that MTTP contributes to dyslipidemia and NHE3 contributes to hypertension both observed in the obesity and that constitutes the risk factors for cardiovascular diseases. Besides, all of these alterations might be linked to the reduction of PKA and PCK activities, at least for the NHE3, whose activity is known to be decreased by PKA.

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P584

Effect of gastrointestinal hormones on bone metabolism after bariatric surgery

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Introduction
In vitro and animal studies have suggested that changes in the secretion of ghrelin, PYY, GLP-1, GLP-2 can influence bone metabolism. An increase in osteoblastic differentiation has been observed after the administration of ghrelin and GLP-1. GLP-2 has been associated with a decrease in bone resorption and PYY inversely with markers of bone formation.
Objective
To analyze the association of gastrointestinal hormones with changes in bone mineral density (BMD) and markers of bone resorption after metabolic gastric bypass (mRYGB), Sleeve Gastrectomy (SG) and Greater Curvature Plication (GCP).
Material and methods
Prospective, controlled and randomized study in patients with type 2 diabetes and morbid obesity. Forty-five patients aged 49.4 years, BMI 39.4 $\pm$ 1.9 kg/m^2, were randomized to mRYGB, SG and GCP. Body composition, BMD and phospho-calcium metabolism, initially and at 12 months were studied. Standard meal test with determination of glucose, insulinemia, GLP-1, GLP-2 and fasting analysis of PYY, ghrelin and glucagon were performed before and at 12 months after surgery.
Results
At 12 months after surgery, the percentage of BMD loss in the lumbar spine (LS) was higher after mRYGB compared to SG and GCP (7.29 $\pm$ 4.6 vs. 0.48 $\pm$ 3.9 vs. 1, 2 $\pm$ 2.7%, $P < 0.05$) with similar findings at the femoral neck. The concentrations of osteocalcin were higher after mRYGB. The secretion of GLP-1 and GLP-2 increased after surgery, but only significantly in mRYGB. Before surgery, PYY and glucagon correlated with CMO (bone mineral content) in LS ($r = 0.325$, $P = 0.044$ and $r = 0.374$, $P = 0.018$). One year after surgery, the AUC for GLP-1 was associated with BMD in LS ($r = -0.335$, $P = 0.049$) and ghrelin with CMO at that level ($r = -0.41$, $P = 0.010$). In the regression analysis, the type of surgery was the main determinant of the decrease in BMD but not the hormonal changes.
Conclusions
Changes in gastrointestinal hormones seem to play a role although not relevant in bone metabolism after bariatric surgery.

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P585

Relationship between human adipose tissue autophagy, obesity and glycemic status

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Introduction and aims
Autophagy is an essential process for cell homeostasis that implies recycling and degradation of damaged organelles and long-lived proteins. It is induced during caloric restriction (in order to obtain energy) or other stress-inducing conditions. Autophagy is initiated by autophagosome formation, a double-membrane vesicle which engulfs cellular components and delivers them for degradation by fusing with lysosomes. Thus, proper autophagy regulation favours cell survival thanks to the turn-over of damaged organelles and energy supply. Although obesity is frequently associated with other metabolic diseases, there are also non-diabetic obese subjects as well as diabetic or insulin-resistant non-obese individuals. For this reason, it has been suggested that functional state of adipose tissue (AT) rather than AT size is which determines the development of metabolic disorders. Despite the fact that previous associations have been described between AT autophagy activation and obesity and diabetes, these paradoxical phenotypes have not been studied, and it has only been analyzed a few of the molecules implied in AT autophagy regarding obesity and carbohydrate disorders in human studies.Thus, the aim of this study was to analyze AT gene expression of molecules implied in the different steps of autophagy according to the degree of obesity and the glycemic status.
Methods
The expression of genes implied in the different steps of autophagy in visceral and subcutaneous AT (VAT and SAT, respectively) was analyzed in the study subjects classified according to their BMI in lean, oeverweight, obese and morbidly obese subjects and to their glycemic status (defined by glucose levels and the insulin resistance index HOMA-IR) in diabetic/high-insulin-resistant subjects (D/HIR) and low-insulin-resistant subjects (LIR).
Results
Comparisons between D/HIR and LIR subjects paired by BMI showed a diminished VAT and SAT expression of genes related to autophagosome formation in patients with alterations in glucose metabolism which was more noticeable in morbidly obese subjects. Significant differences regarding BMI were only found in LIR subjects, having LIR lean subjects higher VAT and SAT expression of these genes than LIR subjects with higher BMI. Gene expression of molecules implied in autophagosome induction and elongation correlated significantly and negatively with HOMA-IR and BMI.
Conclusion
Low autophagy induction in AT is related to a higher susceptibility to insulin resistance and diabetes development which is more noticeable in extreme obesity.

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P586

A newly inflammatory marker in overweight patients: triggering receptor expressed on myeloid cellls-1

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Introduction and aims
Triggering receptor expressed on myeloid cells 1 (TREM-1) is secreted by macrophage and neutrophils in adipose tissue to released pro-inflammatory chemokines and cytokines. TREM-1 activate Janus kinase 2 (JAK2), protein kinase B (PKB/AKT) and extracellular signal related kinase (ERK1/2) pathways and upregulate the expression of genes involved in the inflammatory response. We aimed to indicate associations with serum TREM-1 levels, total sulfhydryl (SH) and malondialdhyde (MDA) levels in overweight patients.
Materials and methods
Twenty overweight patients (OG) and 20 age-matched healthy subjects (CG) (BMI 27.4 ± 1.2 vs 21.9 ± 2.3 kg/m^2, $P = 0.0001$, respectively) were included in our study. Anthropometric measurements were performed by bioelectrical impedance (TANITA BC-420 MA). All complete blood count, biochemical and hormonal analysis associated with obesity were performed by automatic analyzer. Serum TREM-1 levels, MDA and SH levels were measured by Elisa. Homeostasis model assessment (HOMA-IR) was used as a formula: Fasting insulin (mU/l)xfasting glucose (mmol/l)/22.5
Results
Serum TREM-1(225.1 ± 313.1 vs 45.2 ± 17.0 pg/ml, $P = 0.046$, respectively) and SH levels (75 ± 148.9 and 31.7 ± 18.7 µmol/l ($P = 0.033$), respectively) in OG significantly higher than CG. There was no significant difference in serum MDA levels. HOMA-IR in OG was significantly higher than CG (3.2 ± 3.4 vs1.9 ± 1.6). A positive correlation was found between TREM-1 and fat mass ($r = 0.412$, $P = 0.008$).
Conclusions
We first demonstrated to high serum TREM-1 level might early inflammatory marker in overweight patients.

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P587

Pre-operative evaluation of obese patients admitted for bariatric surgery: observations suggesting the introduction of a detailed screening for thyroid diseases

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Background
So far, guidelines for bariatric surgery do no recommend the universal screening for thyroid diseases, except the TSH measurement in selected patients. However, a possible interplay between obesity (possibly complicated by obesity-related comorbidities) and thyroid diseases has been postulated.
Objective
Aim of the study was to investigate the prevalence of thyroid diseases in a cohort of obese patients, evaluated for bariatric surgery. Methods in the study period 2014–2017, 88 patients (72 women and 16 men, mean age 43 ± 11 years), with second or third class obesity, were consecutively screened at the Outpatients Clinic for the study of Obesity, University of Insubria. All patients had preliminary psychosocial tests, nutritional, surgical and endocrinological evaluations. Beyond the pre-operative analysis recommended by the international and national guidelines, serum TSH, TPOAb and TgAb levels and neck ultrasound were assessed. When clinically appropriate, further tests, such as calcitonin determination and thyroid fine needle aspiration were performed. Thyroid diseases were classified as thyroid autoimmune disease, nodular disease, goiter, primitive hypothyroidism or hyperthyroidism.
Results
45/88 patients were eligible for bariatric surgery. Data were collected on the whole study-population (88 patients). Interestingly, patients that fulfilled the diagnosis of metabolic syndrome (34%) had higher incidence of thyroid diseases ($P = 0.002$). Forty patients out of eighty-eight patients (45.5%) had thyroid diseases (17 new cases, 42.5%). Among patients with known thyroid diseases, 23% were treated with levothyroxine (mean dose 0.86 mcg/Kg body weight/day). Mean thyroid volume was 16.7 ± 6.5 ml in women and 17.5 ± 2.9 ml in men; mean TSH level was 2.1 ± 1.2 µU/ml. According to the results of thyroid ultrasound, 78% of patients had hypoecogenic pattern, 24% (21/88) had goiter (52% previously undiagnosed), while 35% had nodular disease (31/88, new diagnosis in 55% of cases). Fifteen patients had autoimmune thyroiditis (17%), of which 40% was newly discovered. Two patients had differentiated thyroid carcinoma (one new case).
Conclusion
Prevalence of thyroid diseases, especially goiter (24% vs 10% in the general population), was higher in the study-population than that observed in normal-weight patients. Interestingly a high proportion of thyroid diseases were undiagnosed. Moreover the incidence of thyroid diseases was higher in patients with metabolic syndrome. Consistent evidences from large trials are warranted. According to these preliminary data, we suggest the introduction of detailed thyroid screening in pre-operative evaluation of obese patients admitted for bariatric surgery.

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P588

Strength training results in reduced fat accumulation and improved blood lipid profile even in the absence of skeletal muscle hypertrophy in obese rats induced by high-fat diet

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Obesity is a chronic multifactorial disease characterized by accumulation of body fat and is associated with a number of comorbidities, such as diabetes and cardiovascular disease. The treatment of obesity depends to the severity of the disease, however, healthy eating with caloric restriction and physical activity are important strategies. In the present study, we aimed to evaluate the effect of obesity associated with strength training on skeletal muscle morphology, body adiposity and metabolic parameters in a rodent model. 58 male Wistar rats were randomized into two groups: control, fed standard diet (C), and obese, fed a high fat diet (49.2% fat) (Ob). The experimental protocol consisted of 28 weeks, being divided into three moments: M1) induction to obesity; M2) maintenance of obesity and; M3) strength training protocol. After the maintenance of obesity period, animals were randomized into two new groups. Thus, the study was finally composed of four groups: sedentary control (CS), control submitted to the strength training protocol (CT), obese sedentary (ObS) and obese submitted to strength training protocol (ObT). Strength training was performed on a ladder 3 times a week for 10 weeks. High-fat diet was efficient to induce animals to obesity in the second week of the experimental protocol, initiating the period of exposure to obesity. Training protocol did not result in hypertrophy of soleus, tibialis, plantar and FHL skeletal muscles, as neither wet and dry muscle weight nor fiber cross-sectional areas were different among groups. The training protocol used was efficient to increase absolute strength, but the capacity to produce strength seems to be impaired in obesity when relative strength was evaluated. Body weight gain was lower in the groups submitted to strength training compared to sedentary groups (ObT vs ObS, CTF vs CS). High-fat diet-induced obesity resulted at higher body adiposity and blood leptin levels but this was attenuated by training. ObT group presented lower total body fat, adiposity index and blood leptin levels compared to ObS group. ObS blood triglycerides were higher compared to CS and CT, but training reversed this effect in ObT group. Blood total cholesterol and HDL were not different among groups. Therefore, the strength training in obese rats promoted metabolic adaptations and reduction in adiposity even in the absence of muscle hypertrophy.

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P589

Association between Leptin gene polymorphisms and plasma leptin level in three consanguineous families with obesity

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Leptin (*LEP*) gene is one of the most promising candidate genes for obesity. The aim of this study was to investigate the impact of *LEP* polymorphisms on obesity, anthropometric and biochemical parameters in a sample of three Tunisian consanguineous families with obesity. Seven single nucleotide polymorphisms (SNPs) in 5′ region of *LEP* gene were genotyped in three consanguineous families including 33 individuals. The previously reported *LEP* SNPs (H1328084, H1328082, rs10487506, H1328081, H1328080, G-2548A and A19G) were evaluated by PCR-RFLP and direct sequencing methods. Single SNP association and haplotype association analyses were performed using the family-based association test (FBAT). To determine allele frequencies of these SNPs in general population, 52 unrelated individuals from the general Tunisian population were also analyzed. Our results showed that H1328084 and A19G SNPs were associated with plasma leptin level (H1328084: A > G, $Z=2.058$, $P=0.039$; A19G: G > A, $Z=2.058$, $P=0.039$). When haplotypes were constructed with these two markers, the risk AA haplotype (frequency 57.1%) was positively associated with plasma leptin level ($Z=2.058$, $P=0.039$). Moreover, SNPs H1328084 and A19G are predicted to modify transcription-factor binding sites. In conclusion, our study provided that two functional variants in 5′ regulatory region of *LEP* gene are associated with plasma leptin level as a quantitative trait. It suggested that H1328084 and A19G have an important role in regulating plasma leptin level.

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P590

Quality of life after sleeve gastrectomy

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Aim
Morbid obesity associated with obesity-related diseases has a negative impact on the quality of life. The aim of the study was to assess the impact of bariatric treatment on the quality of life among patients with morbid obesity who underwent sleeve gastrectomy.
Methodology
Thirty obese patients undergoing sleeve gastrectomy were included in our study. Their weight, height, body mass index were measured at baseline and 6 months after surgery. The quality of live was assessed, 6 months after sleeve gastrectomy by the baros quality of life questionnaire.
Results
Mean patient age was 36.77 ± 7.82. Eighty percent of the study patients were women. Average excess weight lost at 6 months was 43.53%. The score obtained by patients in the questionnaire about the improvement in the quality of life showed excellent (7%), very good (37%), good (36%), fair (13%) and failure (7%) results. There was clinical improvement after surgery in all comorbidities investigated. An association ($r=0.564$, $P=0{,}001$) was found between the Baros score and the excess weight lost.
Conclusion
The weight loss was critical to improve the quality of life of patients submitted to sleeve gastrectomy and led to the improvement of the associated comorbidities.

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Folic acid status in morbidly obese patients seeking sleeve gastrectomy

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Background
A high prevalence of vitamin deficiencies in obese subjects has been reported. Bariatric surgery is the most effective long-term treatment of morbid obesity, but this treatment can result in secondary vitamin deficiency.
Aim
The aim of our study was to evaluate the folic acid status in obese patients before sleeve gastrectomy.
Methods
This was a descriptive study including a population of obese patients reffered to our unit for evaluation for bariatric surgery. Their weight, height, BMI and waist circumference were measured. The basal folic acid blood level were determined. It was considered as normal for levels between 3.89 and 26.8 ng/ml.
Results
Among 30 patients evaluated, females accounted for 80% of the overall sample. Mean patient age was 36.8 ± 7.8 years. Average weight was 137.38 ± 24.32 kg. Average BMI was 50.38 ± 8.58 kg/m^2. Average waist circumference was 138.23 ± 14.97 cm. Mean folic acid blood level preoperatively was 5.03 ± 3.28 ng/ml. About half of the patients (43%) had a folic acid deficiency. Average caloric intake was 3944.53 ± 1683.41 kcal/day. Mean folate intake was 187.87 ± 102.01 µg per day. It was insufficient in 93% of patients. A statistically significant association was found between the folic acid blood level and the daily folate intake. The correlation analysis between anthropometric parameters and folic acid blood level did not show a signifivant statistical association.
Conclusion
Our data suggest that Obesity is a risk factor for folic acid deficiency. This deficiency is likely to worsen after bariatric surgey. Thereby, a preoperative nutritional assessment is important to detect and correct Folic acid deficiency.

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P592

Activation of p53 with low doses doxorubicin reduce the acumulation of lipids in two *in vitro* models of liver steatosis

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Introduction
p53 is transcription factor widely known because of its antitumoral actions. New evidences suggest that p53 also play a key role in the regulation of metabolic homeostasis and specifically in the lipid metabolism.
Objective
We hypothesize that the chemical activation of p53 with low doses of doxorubicin could ameliorate the lipid metabolism in *in vitro* models of liver steatosis.
Methods
We treated with low concentrations of doxorubicin two human hepatic cell lines, HepG2 and THLE-2, exposed to oleic acid to induce lipid accumulation. Furthermore, we administered doxorubicin to HepG2 cells downregulating p53 with siRNAs.
Results
The doxorubicin treatment reduced the lipid accumulation in two human hepatic cell lines in a p53-dependent manner. The drug stimulated the lipid oxidation and inhibited the *de novo* lipogenesis at concentrations that did not affect the cell viability or apoptosis.
Conclusion
The activation of p53 with low doses of doxorubicin could provide a new strategy to reduce the lipid accumulation in the liver of patients with hepatic steatosis.
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P593

Association of dietary factors and dynamic thiol/disulphide homeostasis in subjects with coronary artery disease

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Background
Enviromental factors such as life style changes and dieatary factors become more important on the background of coronary artery disease (CAD). The thiols were the main part of the non-enzymatic antioxidant system in the body and they are the first defensive molecules in elimination of oxidant agents. As a result, thiol levels may be an earlier indicator for CAD. There is limited data on the relation of dietary factors with thiol/disulfide homeostasis in patients with CAD. Therofore the aim of the study was to evaluate relationship between dietary factors and thiol/disulfide homeostasis in patients with CAD.
Methods
Fifty-four patients diagnosed with CAD and 74 healthy volunteers were included in the study. Blood samples were collected for biochemical markers. Nutrition assessment was done once at the time of recruitment; based on previous two days 24 h dietary recall. Serum thiol/disulfide homeostasis was studied with a new and fully automatic analysis method.
Results
There was no age difference between CAD and control groups ($P=0.08$). Also, presences of hypertension, dyslipidemia were similar in all groups. There were significant differences between CAD and healthy volunteers in native thiol ($P=0.000$), total thiol ($P=0.000$), disulfide/native thiol ($P=0.042$), disulfide/total thiol ($P=0.004$), and native thiol/total thiol ($P=0.005$). There were no significant differences in disulfide levels between two groups ($P=0,61$). Patients with known CAD had similar protein ($P=0.09$) and fat intake ($P=0.08$) but had significantly lower energy ($P=0.002$) carbonhydrate intake ($P<0.001$) and dietary fiber intake ($P=0.001$) as compared to control group. Among vitamins; folic acid, niacin, riboflavin, total B6, vitamin A, vitamin C and beta-caroten were similar in CAD and control group except thiamine. ($P=0.047$). There was significantly lower intake of minerals in CAD. Carbonhydrate intake was correlated with native thiol and total thiol levels in CAD patients. ($P<0.001$ and $P<0.001$ respectively). Protein was correlated with native thiol ($P=0.005$) and total thiol levels ($P=0.001$). Also dietary fiber showed relation with native thiol ($P<0.001$)and total thiol levels ($P<0.001$) but did not show any relation with disulphide levels ($P=0.101$). But fat showed relation with only total thiol ($P=0.029$).
Conclusions
In this study oxidation parameters were decreased in CAD patients. Diet is one of the factor affecting CAD and can be related to the oxidation parameters such as thiol/disulfide homeostasis. Increased dietary fiber consumption is associated with increased antioxidant capacity. Carbonhydrate and total dietary fiber intake are associated with thiol/disulfide homeostasis in patients with CAD.

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P594

Effects of a combined lifestyle intervention on anthropometric parameters and long-term cortisol after 10 and 75 weeks: a longitudinal study

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Introduction
The prevalence of obesity is still increasing and is accompanied by significant health problems. High exposure to glucocorticoids, including the stress hormone cortisol, has been suggested to play a role in the development of obesity and associated cardiometabolic derangements. We previously showed that obese persons are exposed to high long-term cortisol levels as measured in scalp hair. It is not known whether these elevated cortisol levels decrease with weight loss. In order to further investigate this relationship, we assessed the longitudinal effects of a combined lifestyle intervention (CLI), on anthropometric parameters and long-term cortisol in obese patients.
Methods
We enrolled 106 adult obese patients (mean age 42.2 years, 73.6% female, mean BMI 40.3 kg/m^2) who were treated at the Obesity Center CGG (Centrum Gezond Gewicht) between October 2011 and March 2016, and had at least one obesity-related comorbidity. All patients underwent CLI, consisting of guided exercising, dietetics, and cognitive behavioural therapy. Anthropometric parameters (weight, BMI, waist circumference) and hair samples (long-term cortisol) were assessed at intake, after 10 intensive weeks, and at the end of the intervention at 75 weeks. Repeated measures ANOVAs were performed to calculate the change over time in weight, BMI, waist circumference and long-term cortisol.
Results
After 10 weeks of intensive CLI, a significant decrease in weight (-6.01 kg (5.1%), $P<0.001$), BMI (-2.05 kg/m^2, $P<0.001$), and waist circumference (-6.76 cm, $P<0.001$) was found. The decline persisted over time and patients were in general able to sustain the loss at the end of the intervention (weight -6.52 kg (5.5%), BMI -2.21 kg/m^2, and waist circumference -7.28 cm, all $P<0.001$). Long-term cortisol levels decreased from 5.31 pg/mg (95% CI 3.88, 6.74) at baseline to 4.59 pg/mg (95% 3.54, 5.63) at 10 weeks, and to 2.87 (95% CI 2.02, 3.72) at 75 weeks. The decrease in long-term cortisol levels after 75 weeks was significant ($P<0.001$).
Conclusions
After a CLI, which yielded sustained weight loss and a decrease in abdominal fat in patients with obesity, long-term cortisol levels significantly decreased. Further research is needed to investigate whether this decrease in long-term cortisol levels is caused by CLI per se, or due to the reduction in weight and whether this decrease is related to cardiometabolic improvements.

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The preoperative diagnosis of type 2 diabetes in the absence of antidiabetic treatment is associated with a worse performance after gastric-bypass compared to patients without diabetes

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Objectives and methods
The mechanism that explains the different weight response to various treatments in obese type 2 diabetes (DM2) patients, compared to those without diabetes, is still unknown. In order to establish the weight response to Roux-en-Y Gastric Bypass (RYGB), 268 patients with morbid obesity (IMC 45.4$\pm$0.4 kg/m^2) were classified by OGTT as having normal glucose tolerance (Grupo A. $n=107$), prediabetes (Grupo B. $n=96$) and recently diagnosed DM2 (Grupo C. $n=65$). No antidiabetic drugs were given in any patient. Anthropometry, body composition (Bod-Pod) and HOMA-R index were assessed at baseline and 1, 6, 12, 18, 24, 36, 48, 60 and 72 months after surgery in all patients.
Results
The mean nadir BMI (kg/m^2) occurred 24 m after RYGB in group A (28.8$\pm$0.6 kg/m^2) and 18 m after surgery in groups B (28.3$\pm$0.7 kg/m^2) and C (30.8$\pm$0.7 kg/m^2). The mean nadir of percent body fat was greater than 30% in all three groups (A: 33.8$\pm$1.2%; B:35.9$\pm$1.4; C:36.5$\pm$1.3%). The percentage reduction of BMI respect to baseline was lower in group C compared to group A at 24 m (30.3$\pm$3.5 vs. 34.4$\pm$1.3%; $P<0.01$), 36 m (28.1$\pm$4.8 vs. 33.2$\pm$1.6%; $P<0.01$) and 48 m post RYGB (25.7$\pm$3.9 vs. 31.7$\pm$1.3%; $P<0.05$). The percentage reduction in fat mass (%) was lower in group C compared to group A at 12 m (28.1$\pm$1.7 vs. 35$\pm$1.7%; $P<0.05$), 18 m (27.4$\pm$1.9 vs. 36.2$\pm$2.2%; $P<0.01$), 24 m (21.9$\pm$1.6 vs. 33.9$\pm$2.5%; $P<0.01$) and 48 m (13.8$\pm$2.3 vs. 30.3$\pm$3.5%; $P<0.001$). Group A and B did not differ in any parameter. HOMA-R index, which was elevated before surgery in all groups, was normalized after 6 months from RYGB without any differences between the different groups.
Conclusions
After RYGB, and when compared with normal glucose tolerant and prediabetic subjects, patients with DM2 have lower weight loss and fat mass reduction, despite they did not receive any antidiabetic treatment, excluding the participation of this factor. These results suggest that DM2 is associated with poorer results following RYGB. There were no differences between groups in HOMA-R index, suggesting that variations in insulin resistance do not play a role in this phenomenon.

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Investigation of the effect of dietary fat content on obesity and metabolic syndrome in smokers

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Background
Despite the efforts to reduce smoking, unfortunately there is a common belief in society to avoid smoking cessation or quitting smoking for weight control. As well as many negative effects of smoking, people continue to smoke instead of diet and life change. Nicotine plus high fat diet (HFD) induces intramyocellular lipid accumulation and mitochondrial abnormalities in obese mice. There is limited data in the relation of dietary fat content and metabolic syndrome in Turkish smoker population.
Objectives
Therefore the aim of the study is to investigate the relationship between dietary fat content and anthropometric measurements for smokers and non-smokers; as well as the effects of smoking and dietary fat content on obesity, metabolic syndrome.
Methods
In total 211 participants 104 smoker,107 non smoker were included in this prospective cross-sectional study. Venous blood samples were collected after a 12h fasting to determine glucose, high-density lipoprotein (HDL-c), and triglyceride levels. Anthropometric measurements and resting blood pressure were also evaluated. Food consumption was assessed through the 24-hour dietary recall method, and the amount of fat consumed by a single dietician is calculated as low or high. Metabolic syndrome was defined according to the International Diabetes Federation definition guidelines.
Results
There was no relationship between smokers and non-smokers anthropometric parameters except hip circumference. Hip circumference of the non-smokers were statistically higher than smokers ($P=0.02$). HFD and metabolic syndrome were not statistically important both of smokers and non-smokers ($P=0.21$ and $P=0.48$). In non-smokers high fat diet induces poor glycemic control ($P=0.20$). There was no relationship between dietery fat content and non alcoholic fatty liver disease in smokers and non-smokers ($P=0.07$ and $P=0.18$).
Conclusion
We observed that smoking reduced only the hip circumference in smokers. But there is widespread belief that smoking has a positive effect on weight in the community. Smokers did not show improvement in weight control and obesity-related metabolic values. We observed that dietary fat content was not associated with smoking and the metabolic syndrome.

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P597

Food addiction: its prevalence among obese patients

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Introduction
The concept of food addiction, which refers to people who exhibit signs of dependence to some high-fat and high-sugar foods, was recently proposed by applying DSM criteria of substance dependence to eating behavior. The Aim of This *study is* to assess the *prevalence of food addiction* among obese patients.
Material and methods
This is a retrospective hospital record-based study of obese patients followed up in the day hospital and education unit of the department of endocrinology of the CHU Mohamed VI of Marrakech. This study was carried out using a Yale Food Addiction Scale questionnaire (YFAS).
Results
A total of 68 obese patients were analyzed, of which the majority were female, the mean age of presentation in years is 47.16 years. The average BMI was 41.4 kg/m^2. The morbid obesity was noted in 52.9% of the cases. All cases presented either abdominal or visceral obesity. The majority of obese patients were sedentary (65%) and food addiction was found among 35.2% of patients. Nibbling behavior hyperphagia was noted in 44% of cases.
Conclusion
The prevalence of food addiction is higher among overweight and obese patients, patients with certain psychopathological characteristics (depression, Attention Deficit Hyperactivity disorder, and high impulsivity), single patient and in patients with neurobiological *dysregulation of brain reward systems*; It is not currently demonstrated that this disorder is systematically responsible for weight gain and/or obesity. Food addiction is a clinical and multidimensional concept which requires integrated care with psychotherapy, pharmacological and social lines of approach. This concept has also practical implications in terms of prevention and public health.

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P598

Abstract withdrawn.

P599

Deciphering the functional role of host-microbiota interactions on metabolic health induced by Roux-en-Y gastric bypass (RYGB) surgery

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Roux-en-Y gastric bypass (RYGB) surgery results in rapid weight loss, reduced adiposity and improved overall metabolism. These health benefits cannot solely be attributed to the reduced caloric intake, but the exact mechanisms are still incompletely understood. Several studies in rodents and humans demonstrated alterations of the gut microbiota following RYGB, suggesting a crucial role of the host-microbial interactions for the beneficial effects of surgery. This study aimed to assess whether the altered gut milieu composition after RYGB is necessary or even sufficient to promote beneficial effects on energy balance and metabolism in a rat model of diet-induced obesity (DIO). Pilot studies prove that the beneficial effects of RYGB on body composition, food intake and glucose homeostasis are dependent on the gut microbial composition and can be abolished via broad range antibiotic administration via drinking water. Allogenic fecal microbial transfer (FMT) from RYGB-operated to DIO animals mimics the beneficial effects on feeding, adiposity and glucose control without surgical gut reconfiguration. In contrast, FMT from metabolically healthy lean donors to DIO animals shows no beneficial effects on metabolism. These preliminary findings affirm the hypothesis that the altered gut microbiome plays an important functional role in the metabolic improvements after RYGB, and that transferring the altered RYGB-gut milieu into a DIO organism is potent enough to accomplish the beneficial metabolic effects without surgical gut reconfiguration.

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P600

Obesity and dementia: the misleading "obesity paradox"

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Background
Mid-life obesity is a risk factor for Alzheimer's disease (AD). On the contrary, late-life obesity has been identified as a protective factor for dementia. Recent published studies have shown that weight loss predicts and precedes dementia diagnosis by decades. Thus, paradoxical effect of body weight across lifespan, the so called "obesity paradox", might be explained by reverse causality. Structural magnetic resonance imaging (MRI) has been extensively used to characterize healthy and pathological aging. Establishing the relationship between BMI and brain structural changes would help to better understand the effects of adiposity on the brain.
Objectives
We aimed to assess the association between late-life obesity and brain structure considering the potential confounding effect of weight loss.
Methods
We included 131 cognitively normal elderly subjects (mean age: 73.4 ± 6.2 years) with available 3T MRI scan from the *Alzheimer's Disease Neuroimaging Initiative* (ADNI) cohort. Significant weight loss was defined as relative weight loss ≥ 5% of baseline weight. We compared the cross-sectional cortical thickness (CTh) related to the BMI in (1) all the cohort and (2) after the exclusion of individuals with significant weight loss. CTh was extracted using *Free Surfer Software*. All analysis were adjusted by potential confounders (age, sex and APOE genotype).
Results
After a mean follow-up of 50.5 ± 30.5 months, 31 (23.6%) subjects experienced significant weight loss (FWE < 0.05). At baseline, these individuals presented decreased CTh in temporal regions of the right hemisphere (FWE < 0.05). When the whole cohort was included in the analysis, there was a weak, although significant, lineal correlation between BMI and cortical thinning. This association was restricted to the occipital region (FWE < 0.05). Results significantly changed after having excluded the subjects with weight loss. In this context, several clusters of linear association emerged in widespread areas of both hemispheres including occipital, temporal and frontal regions (FWE < 0.05).
Conclusions
Late-life unintentional weight loss is related to cortical thinning. Similarly, late-life obesity is associated with cortical thinning. However, weight loss negatively confounds this association.

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P601

Influence of body weight loss on gait and stability function in patients with obesity

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Objective
In our research we studied changes of gait and balance parameters and falls frequency in obese patients during weight loss.
Materials and methods
We examined 37 patients aged 23–69 years (average age 53.6 ± 11.1 years) with BMI ≥ 35 kg/m^2 (average BMI 40.9 ± 9.3 kg/m^2). All patients received recommendations to adhere hypocaloric diet and perform physical exercises in order to reduce body weight. We evaluated baseline body weight, BMI, the number of falls for 3 months, 10 meters walk test along a flat surface, Romberg test and stabilometry (Stabilan - 01) were conducted.
Results
After 3 months, the average body weight in the group decreased from 124.1 ± 26.6 kg to 118.1 ± 23.4 kg, $P = 0.022$ (95% CI: 2.78, 9.22), the number of falls for 3 months reduced from 0.14 ± 0.34 to 0, $P = 0.023$ (95% CI: 0.02; 0.25), the results of 10 m walk test decreased from 113.0 ± 8.82 m/sec to 105.5 ± 3.03 m/ses, $P = 0.005$ (95% CI: 2.86, 12.14). According to the stabilometry data the coefficient of stability improved from 113.5 ± 9.11% to 104.0 ± 2.16%, $P = 0.012$ (95% CI: 3.035, 16.10), deviation of the pressure center in the sagittal and frontal plane decreased from 113.6 ± 9.1 mm to 104.0 ± 2.2 mm, $P = 0.01$ (95% CI: 3.03, 16.1), the movement speed of the pressure center increased from 113.4 ± 8.9 mm/sec to 104.0 ± 2.2 mm/sec, $P = 0.01$ (95% CI: 3.04; 15.81), speed index changed from 113.0 ± 9.1 to 104.0 ± 2.2, $P = 0.01$ (95% CI: 3.0, 16.1) and overall rating movement reduced from 109.9 ± 6.8 to 104.0 ± 2.0, $P = 0.0037$ (95% CI: 0.5; 11.2).
Conclusion
Weight loss in obese patients is associated with the decline of falls frequency, improvement of gait speed, statics and balance functions.

Keywords: obesity, gait speed, gait stability.
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Magnetic resonance imaging of human supraclavicular brown adipose tissue

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Background
Imaging of brown adipose tissue (BAT) is currently performed with combined positron emission tomography and x-ray computed tomography (PET-CT). Recent studies showed promising imaging features of BAT with magnetic resonance imaging (MRI) through modified 2-point-dixon (mDixon) water-fat separation method. The aim of this study was to establish a reliable MRI-procedure for quantification of BAT volumes and weighted fat-fraction (WFF) and to correlate them to cold-induced thermogenesis (CIT).
Methods
23 healthy volunteers (13 males, 10 females, age 18–47 years) were recruited for this prospective, observational study. Energy expenditure (EE) was measured in supine position by indirect calorimetry during warm conditions and after a mild cold stimulus of 120 minutes. CIT was defined as the difference between EE during cold (EE_{cold}) and warm (EE_{warm}) conditions. MRI was performed on a Siemens MAGNETOM Prisma 3T using mDixon water-fat separation method and T2* relaxation time. MRI was performed twice, once during warm conditions and once during mild cold exposure with a cooling vest. Volumes of supraclavicular BAT-depots ($_{sc}$BAT) and WFF were calculated by manual segmentation using ITK-Snap. Primary Endpoint was correlation of $_{sc}$BAT volume with CIT. Data were analysed in R/R-Studio and are given as mean ± standard deviation.
Results
Mean Volume of both $_{sc}$BAT was 71.4 ml ± 39.4 ml. Mean WFF was 74.2% ± 6%. Mean EE_{warm} was 1638 kcal/day ± 362 kcal/day and EE_{cold} 1794 kcal/day ± 408 kcal/day. Mean CIT was 156 kcal/day ± 133 kcal/day respectively 8.5% ± 9.6% of $EE_{warm.}$ Contrary to our assumption, we found no correlation between the volume of $_{sc}$BAT and CIT ($r = 0.05$, $P = 0.87$) or between WFF and CIT ($r = 0.13$, $P = 0.66$). $_{sc}$BAT volume correlated however significantly with increasing age ($r = 0.59$, $P = 0.003$), body mass index ($r = 0.53$, $P < 0.0001$) and WFF ($r = 0.39$, $P = 0.0016$).
Conclusion
Despite the correlation between MRI and glucose uptake of human brown adipose tissue in recent studies, our study found no correlation between the volume and WFF of BAT to cold induced, non-shivering thermogenesis. Thus, MRI without tracer-based molecular imaging is currently not a promising tool for determining the metabolic activity of human brown adipose tissue.

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Benign symmetric lipomatosis (Madelung's disease)

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Multiple benign symmetric lipomatosis (Madelung's disease, Launois–Bensaude syndrome) is significantly rare disease characterised by symmetrical focal deposition of adipose tissue in the neck, upper part of the arms, back, pelvis, and thigh. Although its etiology is uncertain, it has been associated with genetic factors, mitochondrial inheritance and alcoholism. Its pathogenesis seems to include a dysfunction of cAMP and levels of catecholamines in adipocytes. This condition is an important differential diagnosis from obesity. Long-term large lipomatous deposits are cosmetically deforming, and the upper aerodigestive tract and great veins may be compressed. Patients do not effectively lose subcutaneous adipose tissue from lifestyle changes and recurrence after lipectomy is highly frequent. This report presents six cases of non-related patients diagnosed with benign multiple symmetric lipomatosis. Case 1: A 28-years-old, Afro-American woman presented with a mass deposition in the back and neck (horse collar) since her 8 years of age and later associated with polyneuropathy. Her father has similar condition. The patient was treated with lipectomy twice with recurrence. Case 2: A 36-years-old woman without family history presented with mass deposition in the neck and back, observed since 30 years old. Also clinical and karyotype findings confirmed Down's syndrome. The patient has refused surgical treatment. Case 3: A 55-years-old woman, with no comorbidities nor family history, presented with fat deposition in both upper arms, evident for 15 years. Case 4: A 31-years-old woman, with no family history and no other comorbidities, presented deposition in both arms and the back of the neck (humpback) evident since 20 years old. Case 5: A 32-years-old woman, alcoholic, with family history of Madelung's disease presented mass in the neck and armpit from 8 years ago. Case 6: A 53-years-old man, alcoholic for seven years, with no family history, presented deforming fat deposition in the neck and upper chest evident seven years ago. He has refused surgical treatment and ceased alcoholism. In all patients, CT findings confirmed the presence of fat deposits. These cases illustrate the variability of clinical presentation of benign multiple symmetric lipomatosis. Fat deposition site could vary. Association with polyneuropathy, alcoholism, dyslipidaemia, Down's syndrome and different inheritance patterns were present. Nevertheless, none of the cases presented diabetes, hypertension, epilepsy or neuromuscular disorders. In summary, the reported cases support the idea that such syndrome may have intervening factors inducing a variety of distinct phenotypic patterns.

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DXA Body Composition with Visceral Fat analysis improves categorization of the metabolic diseases risk

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Introduction
Many people suffered diverse diseases associated to central obesity. Actually the most frequent tool to estimate the abdominal fat is waist perimeter. In the past and the DXA software was adapted to measure fat content in abdominal region but the visceral and subcutaneous fat couldn't be differentiated.
Objective
Evaluate all tools available and establish the most sensible to discriminate the patients whose had risk to suffer metabolic diseases associated to central obesity.
Methods
Eighty eight patients (26 men, 62 women), were derivatives for endocrinological assessment. Clinical parameters were evaluated as systolic blood pressure and waist perimeter (WP) and biochemical parameters such as glycemia; insulinemia; Homa index; total cholesterol; HDL; LDL; Triglycerides. Total body composition scans using GE-iDXA model device was used. Analysis of the whole-body DXA scans was performed using specific CoreScan software (Version 14.1). We analyzed DXA variables (Total fat mass –TFM-; abdominal fat mass –AFM-visceral fat –Core-Vat- VFM-; and anthropometrics variables (BMI; WP)divided by gender. The continues were analyzed by T-Test (mean) and a regression tests were applied to evaluate the correlations, with a value of $P<0.05$ as significant.
Results
Forty eight were non metabolic affected (all biochemical parameters were normal, they were "Control"), 40 were classified as metabolic affected (Insulin Resistance; Metabolic Syndrome; dyslipemia). There was not statistical difference in age between normal and patients. We stratified by gender and analyzed the results comparing affected to non-affected. Women group showed all parameters significantly higher in patients group (WP: 92.8 vs 81 cm; TFM 36.238 vs 27.105 kg; AFM: 3.108 vs: 2.170 kg; VFM: 1.037 vs 0.534 kg) Men group had not significant differences at TFM (29.695 vs 24.399 kg – $P=0.08$) and were significantly higher the follow parameters: AFM: 2,940.3 vs: 2.137 kg; VFM: 1.385 vs 0.922 kg). Insulin and HOMA Index showed stronger correlations to abdominal fat measured by DXA (Insulin to: to AFM: R2; 0.598; VFM: R2 0.642; VFD: R2 0.682; HOMA to AFM: R2; 0.598; VFM: R2: 0.642) than the correlations with anthropometrics parameters (Insulin To WP R2: 0.200; HOMA index: R2: 0.218).
Conclusion
The anthropometrics parameters are useful but under estimate the prevalence of metabolic diseases related to central obesity, we propose combine with DXA measurements to improve the patients categorization.

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P605

Influence of sleeve gastrectomy on leptin to adiponectin ratio in severely obese adults: A prospective cohort study

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Background
Bariatric surgery is known to dramatically increase insulin sensitivity in severely obese adults. However quantifying insulin sensitivity in these patients with methods such as the hyperinsulinaemic euglycaemic clamp is technically challenging. The leptin to adiponectin ratio (LAR) has previously been validated as a measure of whole body insulin sensitivity. Leptin is a known mediator of metabolic and cardiovascular complications of obesity. Adiponectin has anti-atherogenic, antidiabetic, and anti-inflammatory properties. The influence of bariatric surgery on LAR has not previously been described.
Aim and objectives
We sought to determine changes in LAR over 12 months in severely obese adults undergoing sleeve gastrectomy.
Methods
We conducted a single-centre, prospective cohort study of all patients undergoing sleeve gastrectomy between September and December 2016. Anthropometric data, metabolic profiles, leptin and adiponectin levels were collected before and one year after surgery. Leptin and adiponectin were both measured using the two-site micro titre plate-based DELFIA assay. Data are presented as means $\pm$ standard deviation. Comparisons between baseline and follow up measures were performed using a paired *T*-test.
Results
Twenty-five patients underwent surgery, and 17 of these (12 female, 9 with diabetes mellitus (DM) (defined as baseline HbA1c $\geq$ 48 mmol/mol)) attended for follow up at 12 months and were included in analyses. Mean age was 52.2 ± 8.3 (range 39–71) years. Mean follow up interval was 12 ± 1 (range 10–13) months. Weight reduced from 130.5 ± 30.8 kg to 97.5 ± 21.6 kg ($P<0.001$), BMI from 46.8 ± 7.8 to 35.3 ± 7.2 kgm^{-2} ($P<0.001$), excess body weight percentage from 87.5 ± 31.2 to 41.3 ± 28.8% ($P<0.001$) and alanine aminotransferase reduced from 33.8 ± 16.6 to 15.7 ± 5.5 mmol/l ($P<0.001$). Overall, HbA1c did not change, with baseline and follow up values of 50.5 ± 16.2 and 44.5 ± 13.2 mmol/mol, respectively ($P=0.12$), with a non-significant trend to reduction in DM patients from 62 ± 13.2 to 53.3 ± 11.8 mmol/mol ($P=0.081$). Overall, leptin came down from 40.6 ± 24.8 to 30.8 ± 30.4 ng/ml ($P=0.16$) and adiponectin increased from 4.48 ± 1.58 to 8.92 ± 6.36 µg/ml ($P=0.004$) while LAR came down from 8.88 ± 4.76 to 5.26 ± 6.52 ng/µg ($P=0.036$) and in DM patients from 8.2 ± 3.5 to 5.1 ± 3.2 ng/µg ($P=0.038$).
Conclusion
These preliminary data from a single centre study suggest that relatively high levels of insulin resistance, as evidenced by high LAR, are reduced 12 months after sleeve gastrectomy, both in patients with and without DM. Further studies are warranted to determine whether LAR can serve as a useful prognostic test or an indicator of metabolic response to bariatric surgery.

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P606

Differences in percentage of weight loss and secondary effects after one and two months of treatment with liraglutide versus naltrexone/bupropion

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Introduction
Obesity is one of the most prevalent health problems in our society. The marketing of Liraglutide and the Naltrexone/Bupropion combination has been given the green light.
Objectives
To analyze the differences in a series of 19 patients assigned to treatment with Liraglutide or Naltrexone/Bupropion.
Material and methods
A descriptive analysis was carried out using Stata. 19 patients were included, 9 were treated with Liraglutide and 10 with Naltrexone/Bupropion. We analyzed the percentage of weight loss and side effects at one month and two months after treatment initiation.
Results
Of the 9 patients included in the Liraglutide arm, 2 were male and 7 were female, with a mean age of 56.22 and a mean BMI of 41.35. From the Naltrexone/Bupropion group, 5 male and 5 female participants, with a mean age of 52.90 and an initial BMI of 34.40. After one month of treatment, a % weight loss of 3.81 was observed for the Liraglutide group versus 1.06 for Naltrexone/Bupropion (difference of means 2.75). After two months, a 7.51% weight loss was observed for Liraglutide versus 0.12% for Naltrexone/Bupropion (mean difference 7.40), the latter being statistically significant. 77.8% of patients treated with Liraglutide developed secondary side effects at the first month (28.57% at the second visit), only one patient withdrew from taking the drug. In the Naltrexone/Bupropion group, side effects were observed in 20% with two dropouts for this reason (another 4 abandoned the treatment for other reasons). Regarding the dosage of Liraglutide per month, 11% of Liraglutide 1.2 mg, 33% 1.8 mg, 33% 2.4 mg, 22% 3 mg. At two months, 43.86% 1.8 mg and 57.14% 3 mg.
Conclusions
In our clinical practice we observed a greater weight loss % in the Liraglutide group, especially at two months of treatment. The number of negative side effects was greater for Liraglutide, primarily in the first month, with a higher abandonment rate for Naltrexone/Bupropion.

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P607

Prevalence of obesity in a population of patients with HIV: relationship with clinical lipodistrophy, effect of sex, age, viral replication, duration of disease and cart

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Introduction
Adipose tissue disturbances (lipodystrophy and obesity) are prevalent in patients infected with HIV. Our aims were to evaluate the prevalence of obesity and the association with lipodystrophy, the effect of gender, age, viral replication, duration of disease and cART in a population of HIV patients under cART.
Methods
In this retrospective study, 580 patients were included. The characteristics of the population are presented through percentage, mean and standard deviation. For comparison, *t*-test and chi-square test were used. Logistic regression model was used to adjust the confounding factors. Patients were classified according to the prevalence or absence of clinical lipodystrophy and in 4 categories of body composition: 1) without lipodystrophy (without lipoatrophy and without abdominal prominence-AP); 2) isolated AP; 3) isolated lipoatrophy; 4) mixed forms of lipodystrophy (with lipoatrophy and with AP). AP was defined according to the waist circumference criteria of the IDF.
Results
Of the 580 HIV patients (414 men), 5.17% were underweight, 40.69% normal weight, 34.66% overweight and 19.48% obese; 15.4% had no lipodystrophy; 30.62% isolated AP; 27.17% isolated lipoatrophy and 28.1% mixed form of lipodystrophy. In obese patients, clinical lipodystrophy was present in 28.6%, being significantly lower in patients with excess weight [odss ratio (OR) = 0.12; 95% CI] and in those with obesity [OR = 0.32; 95% CI], when compared with those of low weight, regardless of sex, age, duration of cART, HIV or viral load. There was an association ($P < 0.001$) between BMI and body fat categories. The presence of lipoatrophy decreases with increasing BMI: in patients with low BMI, 24.1% had no lipodystrophy and 72.41% had lipoatrophy alone; in those who were overweight, most had mixed forms of lipodystrophy (41.24%), and AP was also common (39.69%); in those with obesity, most of them (70.3%) had isolated AP. The prevalence of obesity was not influenced by viral suppression, sex, age, duration of HIV infection or cART.
Conclusion
In this population of patients infected with HIV, excess weight, obesity or some degree of alteration in the distribution of body fat were very prevalent. The presence of clinical lipodystrophy was lower in overweight and obese patients than in those with low weight regardless of gender, age, duration of cART or infection with HIV and viral load. Patients with obesity had lower viral suppression, and the prevalence of obesity was not influenced by sex, age, duration of HIV infection or cART.

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Paediatric Endocrinology

P608

rs1800497 polymorphism of the DRD2 Gene assosiation with plasma leptin and dofamine Levels in obese and lean children

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Background and aim
The TaqI (rs1800497) polymorphism of the Dopamine Receptor type 2 (DRD2) gene allele has been commonly related to increased ad lib food intake, weight gain, and risk for obesity overeating and risk for obesity. We supposed to find associations between body mass index (BMI), the TaqI (rs1800497) polymorphism of the Dopamine Receptor type 2 (DRD2) gene and plasma leptin and dopamine in children with alimentary and extreme obesity and normal weight.
Materials and methods
Retrospective analysis in 288 children aged from 0,4 to 17,9 years were performed in children who appealed to endocrinologist for medical aid from 2009 to 2015 y. 179 children were randomly genotyped in the rs1800497 of DRD2 gene. Children were split up in terms of BMI into 3 groups: the 1st – normal weight (NW) (± 1 S.D.S., $n = 30$), the 2nd – alimentary obesity (AO) ($\geq +2$ S.D.S. $< +4$ S.D.S., $n = 98$), the 3rd – extreme obesity (EO) ($\geq +4$ S.D.S., $n = 160$). Plasma dopamine (D) and leptin (L) concentrations were detected by enzyme-linked immunosorbent assay (ELISA). According to percentiles of D levels children were divided to 4 groups: the 1st – patients with low D levels (< 4.99 pg/ml); th 2nd – decreased D (4.99 – 11.64 pg/ml); 3rd – increased D (11.65 – 60.0 pg/ml); 4th – high D levels (> 60.0 pg/ml). Analogically patients were split up depending on L concentrations: the 1st – low L (< 13.15 ng/ml); the 2nd – decreased L (13.15 – 23.78 ng/ml); the 3rd – increased (23.79 – 40.18 ng/ml); the 4th – high L (> 40.18 ng/ml). Statistical analysis were performed by means of SPSS 21.0 (χ^2-criterion, likehood ratio) ($P < 0.05$).
Result
Children with NW had 6.7% of high D levels, 40% - decreased D, in comparison with EO group who had 32% patients with high D concentrations and 28% - increased D ($P = 0.038$). There were found out L levels differences: 86.7% children with NW had low L; 34.7% patients with AO L levels were increased; 31.5% children with EO had high L concentrations and only 17.7% had low L ($P = 0.0001$). Children with AO and EO had raised A1 TaqI DRD2 allele frequencies: in 45.5% equally in contrast with NW patients (9.1%) ($P = 0.012$). There were not any links between A1A1 genotype, plasma D and L concentrations.
Conclusions
A1A1 allelic variant of TaqI (rs1800497) DRD2 polymorphism were significantly associated to plasma leptin and dopamine concentrations and BMI ($P = 0.012$, $P = 0.038$, $P = 0.0001$ respectively).

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P609

The correlation between urinary ketosis and metabolic indices in healthy young adolescents of Korea

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Background and aims
The prevalence of metabolic syndrome in Korean youth population has been increased by introduction of Western diet in the past decades. The aim of this study was to investigate the incidence of urinary ketosis and correlation with metabolic indices in healthy adolescents in Korea.
Materials and methods
This was a large-scale, community-based study conducted from January 2007 to December 2010. A total of 1,349 subjects (749 males and 600 females) aged 15 through 19 years without history of diabetes were enrolled. Urine ketone was analyzed by semi-quantitative dipstick method.
Results
The prevalence of urinary ketosis was 24.2% (21.6% in male and 27.5% in female). The presence of urinary ketosis was negatively correlated with fasting glucose, fasting insulin, HOMA-IR, and triglyceride level, and positively correlated with HDL-cholesterol in males ($r=-0.086$, -0.095, -0.090, -0.084 and 0.100 respectively, all $P<0.05$), and females ($r=-0.124$, -0.189, -0.185, -0.141 and 0.134 respectively, all $P<0.05$).
Conclusion
Urinary ketosis was common in Korean healthy adolescents. Urinary ketosis was correlated with more metabolically healthy profiles in this population.

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P610

Peculiarities of functional activity of thrombocytes in adolescents with diabetes mellitus tipe 1

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Thrombocytes play important role in pathogenesis of diabetic vascular complications.
Aim
To study peculiarities of functional activity of thrombocytes in adolescents with diabetes mellitus type 1 (T1DM).
Patients and methods
98 adolescents (42 boys, 56 girls) 12–16 y.o. with T1DM were examined. The duration of the disease was: less than 1 year in 25 patients (HbAc1 $7.4\pm0.3\%$) – group 1, from 1 to 5 years in 40 patients (HbAc1 $8.9\pm1.2\%$) – group 2, more then 5 years in 33 patients (HbAc1 $10.3\pm1.7\%$) – group 3. Control group: 40 healthy adolescents 12-16 y.o. The indexes of trombocyte aggregation (degree, speed and time of aggregation) measured by laser method with different inductors (ADP, kollagen, adrenalin) and intravascular aggregation were evaluated.
Results
Levels of ADP- and adrenalin-stimulating aggregation, speed of kollagen-stimulating aggregation and intravascular aggregation of thrombocytes were increased in group 1 in comparance of control group ($P<0.05$). Levels of ADP- and kollagen-stimulating aggregation ($P<0.05$) and intravascular aggregation ($P<0.001$) were also increased in group 2. Decrease of aggregation time was revealed in this group ($P<0.05$). Increase of all indexes of functional activity of thrombocytes ($P<0.05$) and increase of intravascular aggregation ($P<0.001$) were found in patients of group 3 in comparance of control group.
Conclusions
Functional activity of thrombocytes in adolescents with T1DM appeared to increase in correlation with duration of the disease and it may demand treatment with heparinoids.

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Steroid Metabolism + Action

P611

Sex differences in glucocorticoid-induced metabolic disturbances in mice

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Introduction
Glucocorticoids (GCs) are widely used anti-inflammatory medications that cause many metabolic side effects. Long-term treatment with GCs causes obesity and induces insulin resistance in many metabolic tissues, including adipose tissue and muscle. Factors secreted by adipose tissue, so-called adipokines, including leptin and adiponectin, also regulate the glucose-insulin axis. Obesity increases circulating leptin but decreases adiponectin levels. Despite several studies on GC regulation of adipose tissue function, mass, and distribution, the sex-specific effects of GCs have not been well elucidated. Here, we studied the effects of high-dose corticosterone (rodent GC) on glucose metabolism and circulating adipokines.
Methods
Nine-week-old male and female C57BL/6J mice were implanted with 50 mg corticosterone (Cort) or vehicle (Veh) pellets (6 animals per condition). Ad-lib blood glucose levels were measured every 2 days. Two weeks after implantation, we measured fasting glucose levels, collected blood samples for adipokine measurement, and performed an intraperitoneal glucose tolerance test (IPGTT). Data are shown as mean $\pm$ SD.
Results
Corticosterone treatment increased food intake in both sexes, but increased ad-lib blood glucose levels only in male mice (Veh-male 8.2 ± 0.3 mM, Cort-male 14.8 ± 1.6 mM, Veh-female 7.6 ± 0.4 mM, Cort-female 6.6 ± 0.5 mM; $P<0.001$). Corticosterone strongly increased fasting plasma insulin levels in both sexes (Veh-male 50 ± 17 pM, Cort-male 1071 ± 438 pM, Veh-female 28 ± 5 pM, Cort-female 1104 ± 631 mmol/l; $p_{Cort}<0.001$), but fasting blood glucose levels of both sexes remained within normal range. Corticosterone increased fat mass and serum leptin levels in both sexes. Surprisingly, adiponectin levels were also increased. Female mice had a higher basal adiponectin/leptin ratio than male mice and corticosterone markedly reduced the ratios in both sexes (Veh-male 34 ± 24, Cort-male 1.9 ± 0.3, Veh-female 375 ± 351, Cort-female 3.9 ± 1.4; $p_{Sex}=.035$, $p_{Cort}=.015$). IPGTT showed that corticosterone treatment resulted in blunted peak glucose levels in both sexes but more pronounced in female mice.
Conclusions
Sub-chronic high-dose GC causes insulin resistance without fasting hyperglycemia in both sexes of mice, but causes remarkably high glucose levels in the ad-lib fed condition in male mice only. GCs increase fat mass and alter circulating adipokine levels in both sexes. Adipose tissue adaptation such as an increased adiponectin secretion may be a crucial initial protective mechanism against the GC-induced metabolic disturbances.

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Thyroid Cancer

P612

A case of diabetic patient with recurrent ketosis after U-300 glargine treatment

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Introduction
U-300 glargine is a new generation long acting insulin. Nocturnal hypoglicemia and weight gain with U-300 glargine is lower than U-100 glargine. However, it may take 3–4 days for U-300 glargine to reach stable state in plasma. We report a diabetic case with recurrent ketosis after U-300 glargine.
Case presentation
A 20 years old woman with type 1 diabetes mellitus who uses basal and bolus insulin (U-300 glargine and insülin aspart). She applied to emergency clinic with stomachache, diarrhea and nausea. The patient did not use insulin for a few days because of these complaints. As a laboratory results, plasma glucose concentration: 380 mg/dl, 3 positive ketones in urine analysis, PH: 7,07 in venous blood gas analysis, HCO3: 6 mmol/L. She was hospitalized in intensive care unit with diabetic ketoacidosis. Diabetic ketoasidosis improved after fluid, electrolyte replacement and insulin treatment. Urine examination showed ketones to be negative We started her routine basal- bolus insulin treatment with U-300 insulin glargine and insülin aspart. We observed again ketones (+2 positive) in urine analysis 10 hours later under her routine basal bolus treatment.
Conclusion
U300 glargine use may be associated with ketosis relapse in early period after diabetic ketoacidosis has improved, in this respect the physician must be careful.

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Poster Presentations: Environment, Society and Governance

Diabetes Therapy

P613

Safety and efficacy of the available oral anti diabetic drugs in treating type-2 diabetics during Ramadan1437(Hijri)fasting in Fayoum Governate

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Introduction
Fasting in Ramadan is one of the five pillars of Islam. Without relevant medical advice and intervention, fasting can put patients with T2DM at an increased risk of serious complications. The aim of this study was to compare the effectiveness and safety of available oral anti diabetic drugs in treating type-2 diabetics during Ramadan fasting.
Methods
More than 400 T2DM patients were included in this 16-week prospective study, data were collected up to 6 weeks before and 16 weeks after Ramadan fasting. Patients who had received metformin alone or with sulfonylurea (SU), DPP4-I or TZDs or any combination of the afromentioned were enrolled into the study.
Results
This study concluded that mean total HbA1c improved during Ramadan ($P<0.001$). This study also found that patients treated with SUs experienced major hypoglycemic events Similarly, a fewer patients experienced weight gain when treated with TZDs. On the contrary we found that there was no evidence of hyperglycemia or hypoglycemia in patients using DPP4-I.
Conclusions
There are several potential benefits of fasting during Ramadan. Active glucose monitoring throughout the holy month of Ramadan enabled us to pick up more hypoglycaemic episodes. The study revealed that the preferred antidiabetic drugs during Ramadan are DPP4-I.
Keywords: DPP4 inhibitors, hypoglycemia, sulphonylureas, type 2 diabetes mellitus, TZDs, metformin
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Endocrine Disruptors

P614

Assessment of endocrine disrupting chemical screening using differentiated cardiomyocyte from mES cell

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Endocrine-disrupting chemicals (EDCs) are structures similar to steroids hormones which can interfere with hormone synthesis and normal physiological functions of male and female reproductive organs. EDCs tend to bind to steroid hormone receptors. Sex steroid hormones influence calcium signaling of the cardiac muscle in early embryo-development. Progesterone (P4) has been reported to affect both blood pressure and other aspects of the cardiovascular system. To confirm the affect of progesterone (P4), octyl-phenol (OP) and bisphenol A (BPA) on early differentiation of mouse embryonic stem (ES) cells into cardiomyocytes, the hanging-drop method was performed to form embryoid bodies. The mouse embryoid bodies (mEB) were suspended, attached onto 6 well plates and cultured in differentiation medium containing steroid-free FBS without LIF. P4, OP and BPA were treated at two days after attachment and media were replaced every two days. To investigate the calcium signaling, the mRNA level of calcium channel genes such as Trpv2 and contraction-related genes such as Ryr2, Cam2 and Mlck3 was analysed. In addition, mifepristone (RU486), which is a synthetic steroid that has an affinity for PR, was used to confirm the impact of P4 through PR. To determine if RU486 is capable of attenuating the inhibition effect, RU486 was applied for one day starting on day 11. Trpv2, Ryr2, Calm2 and Mlck3 decreased in the P4-treated group. RU486 treatment led to recovery of the decreased of cytosolic calcium-related genes in parallel with a reduction in the of PR. Treatment of OP and BPA were alter the of calcium channel and muscle-contraction related genes. These findings maybe be useful for screening EDCs during cardiac developmental process.
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P615

Disruption of amelogenesis by Adult Exposure to Di(2-ethylhexyl) Phthalate in Mice

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MIH (Molar Incisor Hypomineralyzation) is a recently described enamel pathology that affects now 15 to 18% of children worldwide. Its prevalence increased similarly to other pathologies associated to exposure to Endocrine Disrupting Chemicals (EDCs). In addition, MIH affects selectively permanent first molars and incisors, the first developing teeth during the perinatal period also the time window with the highest susceptibility to EDCs. Our previous published data showed the bisphenol A (BPA) as a causal factor of MIH. In the present study, we compare the effects of BPA and Di(2-ethylhexyl) phthalate (DEHP) in male mice as both EDCs were widely used by plastic industry and found in many good consumers. Eight weeks-old C57bl6 mice were exposed to increasing dose of DEHP from 0.5 to 50 µg/kg/day during 4 weeks. Clinical observation of continually growing incisors showed 11% of teeth with enamel breakdown and 11% of completely broken teeth. MicroCT analysis revealed increased enamel volume contrary to BPA that decreased enamel volume and mineralization. Ameloblasts forming the dental epithelium are cells in charge of enamel synthesis. Their precise function changes during amelogenesis according to their stage of differentiation. They first secrete enamel matrix proteins (mainly amelogenin and enamelin) determinant for enamel thickness and volume, and second they expression many ion transporters (SLC26A family) and proteases (MMP20 and KLK4) necessary for the terminal and complete mineralization of enamel. RT-PCR analysis of microdissected dental epithelium showed that SLC26A4/pendrin is a common target gene of DEHP and BPA but MMP20 is modulated by DEHP only whereas enamelin by BPA only. In vitro analysis are currently carried out to identify underlying molecular mechanisms. In conclusion our data showed that several EDCs can disrupt amelogenesis but their target genes and mechanisms of action appeared different generating different enamel defects. Characterization of enamel defects may help to reconstitute the history of exposure to pollutants during the perinatal period and use them as early marker of exposure to these molecules.
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Neuroendocrinology

P616

Use of a new classification algorithm based on administrative health databases to estimate incidence and prevalence of acromegaly in Piedmont Region, Italy

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Background and aim
Information on incidence and prevalence of acromegaly usually originates from studies performed in referral endocrine care centers, whose catchment areas do not generally cover the entire population. Administrative databases can provide key information to assess the impact of acromegaly on patients and health systems. Our study aimed at estimating the prevalence and incidence data of acromegaly stratified by age and sex using data obtained in the Piedmont region, Italy.
Methods
A retrospective study was conducted in the Piedmont region from January 1st 2012 to December 31th 2016 using administrative health databases of hospital discharge forms, certification of chronic diseases, drug prescriptions, specialist outpatients, and radiological data. Cases of acromegaly were defined if at least two claims from the four following databases were accomplished: i) hospital records with acromegaly diagnosis code (ICD-9-CM: 253.0); ii) exemptions from co-payment for acromegaly (code: 001); iii) prescriptions for Octreotide LAR, Lanreotide Autogel, Pegvisomant, Pasireotide LAR; iv) prescriptions for pituitary MRI or CT scans. Cases were excluded if subjects received less than three separate drug prescriptions or if carrying a diagnosis different from acromegaly.
Results
In the period 2012–2016, 369 individuals (M = 146, F = 223) were documented in the Piedmont population meeting our criteria for acromegaly. Overall incidence was 5.3 per million population per year (95% CI: 4.2–6.7), and overall prevalence was 83 cases per million inhabitants (95% CI: 75–92). Mean age was 50.9 years. Both incidence and prevalence rates were slightly higher among women (Rate Ratio: 1.08, Prevalence Ratio: 1.43). Age-specific incidence rates were similar in the two sexes up to the age of 39 years but seemed to diverge thereafter, with an increasing trend among men. Prevalence was substantially higher in women between 40 and 80 years of age and increased continuously up to 79 years in both sexes.
Conclusions
This is the first population-based study conducted in Italy to estimate incidence and prevalence of acromegaly. Current results are consistent with the available literature on this topic and show a higher prevalence than previously reported. Even if our algorithm requires proper validation, it could represent a comprehensive tool to describe the pattern of acromegaly, to assess its burden on patients and health care systems, and to provide guidance on resources allocation, especially in countries were national registries on acromegaly are not available.
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Pituitary - Clinical

P617

Living with acromegaly: patient journey in europe vs USA
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Introduction
Patients with acromegaly have often a challenging path from diagnosis to treatment start and to long-term care. Two separate acromegaly patient advisory panels (one in Europe and one in USA) were conducted with the aim to better learn about their experience and how this could be improved. This format was chosen to allow direct patient to patient interactions and to understand possible unmet needs and opportunities within the acromegaly community. An independent moderator facilitated the meetings and discussions.
Findings
In Europe, 7 patients (2 UK, 2 France, 2 Belgium, 1 Spain; 2M: 5F time since diagnosis 2–17yrs) attended, while in US 8 patients (3M, 5F, time since diagnosis 2–10 yrs.) attended. All patients had prior pituitary surgery and were receiving medical treatment. In both groups, most patients reported that their journey was challenging regardless of symptoms or age at time of diagnosis. For the majority of patients, symptoms went unrecognized for years (range 5–15 years) prior to diagnosis and included: headaches, arthralgia, fatigue, cessation of menses, weight gain and changes in physical appearance (US only). The European patients reported that their Health Care Providers (HCPs) were supportive and were generally satisfied with their care once the diagnosis was made. They recognized and accepted that living with symptoms of acromegaly and ongoing treatment will be 'part of life'. However, they would like more connections with other acromegaly patients for support. All US patients were concerned about their QoL and life expectancy; 6/8 reported a disconnect from their HCPs as to perceived control and care. The patient advisors proposed several ideas to improve their experience, i.e. HCP education, patient support, ambassador programs, patient panels and personalized approach.
Conclusions
Hearing directly from patients with acromegaly in an advisory panel setting is an innovative way of learning and understanding outside the traditional clinical setting. We identified differences in patient's experience in Europe vs US especially in acceptance of their disease and perceived care from their endocrinologist. There remains a major need for ongoing education, awareness and resources for patients as well as physicians to benefit their long-term care.
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Thyroid (non-cancer)

P618

Online health information seeking behavior by patients prior to their outpatient appointments in endocrinology
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Background
The internet is becoming an increasingly important medium for health-related information and is considered a means for aiding patient empowerment. Online health information (OHI) seeking behavior has never been studied in the field of endocrinology.
Objective
We set out to examine the frequency, how and why the internet is utilized for health-related information and the impact of such activity. Future information needs were also investigated.
Methods
A cross-sectional mixed-methods study was performed with more quantitative data. Qualitative data underwent thematic analysis. Patients attending a general endocrinology clinic were recruited from two clinical sites. A questionnaire survey was designed to answer our specific research questions.
Results
312 patients were included of which 251 (80.4%) were females; the response rate was 78.4%. OHI seeking was reported by 175 patients (56.1% of the whole study population and 78.1% among those that sought any health-related information); it was commoner among new patients ($P = 0.038$). OHI seekers perceived OHI to be of high quality (135, 77.1%) and demonstrated a good understanding of what constitutes trustworthy information. Notwithstanding, 71 (40.6%) relied on the top search engine options as their main criterion for choosing a website and 104 (59.4%) were not aware of website certification tools like HONcode. OHI seekers sought general information (90, 51.4%); this was confirmed by thematic analysis which also revealed that ease of access and the wealth of information offered by this medium are important reasons why they go online. Among OHI seekers, 63 (36.6%) reported that their behavior changed after seeking OHI

e.g. by improved self-care or compliance. Only 45 (25.7%) of OHI seekers discussed the information they gathered with their endocrinologist. If an interactive e-learning module was available, 194 (62.2%) of the 312 patients expressed a will to use it, especially existing OHI seekers ($P < 0.0001$) and those reporting a need for more health-related information ($P = 0.024$).
Conclusions
OHI seeking is practiced by the majority of endocrine patients before their appointments. Patients have a good awareness of what makes a website trustworthy, but more education and guidance is needed. The reason they seek OHI is because they want to gather more general health information, but are also attracted by the inherent characteristics of the internet. Patients should be encouraged by their doctors to discuss their online gathered information. Many endocrine patients are keen to utilize e-learning modules, even those patients that are not current OHI seekers.

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P619

Overuseoflaboratory and ultrasonographic examinations in thyreidology: Study from the Slovak Republic

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Objectives
Slovakia is gradually implementing health technology assessment (HTA). This method evaluated the issue of possible overuse of laboratory and imaging investigations in thyroidology for the last 10 years. The analysis being divided between 2008–2011 and 2012–2017. In this study we publish the outputs from the first stage phase.
Methods
The study was conducted using data from patient records of the General Health Insurance Company, a.s., 2011 registered approximately 3 400 000 policyholders (64.7%). Laboratory (fT3, fT4, TSH, ATPO, aTG, thyroglobulin, TRAK) and USG thyroid examinations were assigned a diagnosis E.00-E.07.
Results
The number of examined patients with these diagnoses had a permanent growth tendency: 2008 – 168.200, 2009 – 176.349, 2010 – 229.524, 2011 – 240.662. The same tendency was observed in laboratory examinations: 2008 – 414.904, 2009 – 449.500, 2010 – 605.268, 2011 – 620.378, as well as USG examinations: 2008 – 102.212, 2009 – 109.700, 2010 – 148.528, 2011 – 156.775. Year 2011 brought these results in laboratory examinations: fT4 – 196.785, TbG – 1.247, fT3 – 50.701, aTG – 58.139, aTPO – 64.910, TSH – 237.460, TRAK – 11.136. 2008 was similar in all laboratory examinations. The average number of laboratory and USG examinations per patient was – 3.074 examinations, 2009 – 3.171, 2010 – 3.284, 2011 – 3.229 examinations. The cost of these tests was calculated per 1 patient per year. 2008 – € 23.35, 2009 – € 25.59, 2010 – € 25.82, and € 26.76 in 2011. The total cost of these laboratory/USG examinations was in 2008 – 3 070 828/856 093 €, 2009 – 3 263 430/913 730 €, 2010 – 4 388 179/1 238 203 €, and 2011 – 4 223 686/€ 1,308,098.
Conclusions
Proposals for measures to reduce the costs of overuse of these examinations may be different according to the methodology used (based on the costs of 2011 – 4 223 686 or 1 308 098 €): A. When reducing the reimbursement to the level of the Slovak average, the saving would be approximately 442 535 € (8% of total costs). B. The savings would be around 525 130 € for the selected examinations – 9.49%. C. By reducing the average number of laboratory examinations from 3.4 to 3.0, the savings would reach about € 496 705, i.e. 11.76% and in case of USG testing from 1.15 to 1.0, the savings would reach 170 576 €, ie. 13.04%.

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P620

Restless legs syndrome in population of patients with thyroid disease in comparison to general populaton – questionnaire study

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Introduction
Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common condition of the nervous system. It causes an overwhelming, irresistible urge to move the legs, mainly in the evening and night hours. It occurs in 7.2–10.0% of the population of western countries. Etiopathogenesis of RLS is not fully understood, but there is a hypothesis than an important role may play the imbalance between thyroid function and the dopaminergic system. The main aim of the study is to assess the incidence of RLS in population of patients with thyroid diseases and compare its epidemiology to the general population.
Material and methods
In the study we used online survey (based on the Google Spreadsheet mechanism), which was distributed via social media in groups associating patients with thyroid diseases (test group) and outside them (control group). The questionnaire included questions about all of criteria for the diagnosis of RLS, according to the International Restless Legs Syndrome Study Group consensus (2014).
Results
In pilot study based on responses from 94 respondents, a slightly more frequent occurrence of RLS symptoms was found in patients with thyroid disease than in the control group ($\Delta = 1.18\%$, but $P = 0.09$). Research in progress – full results (based on a group exceeding the minimum sample size, i.e. >384 respondents) will be presented during the conference.
Conclusion
Based on the current results of the study, patients with thyroid disease more often report RLS than in the general population. Full conclusions will be presented during the conference.

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Poster Presentations: Interdisciplinary Endocrinology

Adrenal Cortex (to include Cushing's)

P621

Corticosteroid secretion after the soy extract application to orchidectomized adult male rats

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Herein, we have tested the effects of application of commercial soy extract, rich in estrogen-like isoflavones, to orchidectomized adult rats (the model of mild andropause), on the corticosteroid secretion. Exploited animal model provides the opportunity to examine the potential effects of steroid-like compounds in the hormonal milieu deprived of endogenous sex steroids along with preserved hippocampal and hypothalamic regulation of the adrenal gland function. The experimental groups included sham-operated (**SO**), orchidectomized (**Orx**) and soy extract-treated orchidectomized (**Orx**+**Soy**; 30 mg/kg b.m. *s.c.*, for 3 weeks) rats. Plasma level of ACTH and serum levels of aldosterone, corticosterone and DHEA were determined by the immunoassays. **Orchidectomy** caused the increase ($P<0.05$) of circulating ACTH, aldosterone and DHEA by 57.0%, 2.6 and 2.0 folds respectively, compared to **SO** group. In **Orx**+**Soy** group, blood levels of ACTH and corticosterone were higher ($P<0.05$) by 99.5% and 79.6% respectively, in comparison with **SO** group. Also, the treatment of **orchidectomized** rats with **soy extract** elevated ($P<0.05$) the systemic levels of ACTH, aldosterone and corticosterone by 26.9%, 2.7 folds and 56.4% respectively, while the circulating DHEA level was decreased (65.6%; $P<0.05$), all compared to the corresponding parameters in **Orx** rats. Summarily, soy extract raised the ACTH level which has stimulatory influence on the mineralocorticoid and glucocorticoid output, while the adrenal androgens consequently fallen, in the rat model of mild andropause. The data support impression of a beneficial effect of soy isoflavone mixture on the homeostatic response to stress, but also call for precautions in the case of cardiovascular issues presence.

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P622

High prevalence of suppressed adrenal cortical function in kidney transplanted patients during low-dose prednisolone therapy

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Introduction
Maintenance immunosuppressive regimens after renal transplantation (RTx) most often include prednisolone which may induce secondary adrenal insufficiency. Adrenal insufficiency is a potentially life-threatening side effect to glucocorticoid treatment due to the risk of acute adrenal crisis. We aimed to investigate the prevalence of prednisolone-induced adrenal insufficiency in RTx patients receiving long-term low-dose prednisolone treatment.
Material and methods
In a case-control study, 30 RTx patients (17 males, mean age 50.4 s.d. 13.1) treated with prednisolone and 30 dialysis patients (19 males, mean age 59 s.d. 13.1) not treated with prednisolone underwent testing for adrenal insufficiency by a 250 µg Synacthen test. RTx patients were transplanted at least one year before enrollment and receiving continuous treatment with either 5 or 7.5 mg prednisolone/day for at least 6 months before the study. Fifteen peritoneal dialysis (CAPD) patients and 15 haemodialysis patients comprised the control group. The Synacthen test was performed fasting in the morning. Transplanted patients paused prednisolone for 48 hours before the test and all patients ($n=7$) paused locally applied glucocorticoids for as long as possible. Normal adrenal function was defined as P-cortisol $\geq$420 nmol/l 30 min after Synacthen injection, as validated for the local Roche Elecsys® Cortisol II assay.
Results
Of the RTx patients, 13 (43%; CI: 27–61%) had an insufficient response to the Synacthen test compared to one patient in the control group (3%; CI: 0.6–17%) ($P=0.0004$). Insufficient response in RTx patients was seen in 9/25 and 4/5 patients treated with 5 and 7.5 mg prednisolone/day respectively. For the RTx group both baseline P-cortisol and 30 min P-cortisol was generally lower compared to dialysis patients with a mean of 265 nmol/l (s.d. 100) vs 350 nmol/l (s.d. 69) for baseline P-cortisol and mean of 411 nmol/l (s.d. 153) vs 623 nmol/l (s.d. 99) nmol/l for 30 min P-cortisol ($P<0.0001$). No correlation was found between duration of treatment and 30 min P-cortisol ($P=0.68$, $r=0.08$). Of the seven patients treated with local glucocorticoids, 3/4 were insufficient in the transplant group and 1/3 in the control group.
Conclusion
We found a high prevalence of adrenal insufficiency among RTx patients receiving low-dose prednisolone treatment. We therefore advocate for an increased clinical alertness and a discussion of how to manage the risk of adrenal insufficiency in patients with a kidney graft.

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Calcium & Vitamin D Metabolism

P623

Frequency of multiple endocrine neoplasia-1 in patients with primary hyperparathyroidism

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Aim
Multiple endocrine neoplasia-1 (MEN-1) is described in patients as presence of clinical two or more primary MEN-1 associated tumors or patients who have MEN-1 clinics and also have family members with MEN-1 associated tumors. It is associated with loss of activation genetic mutation in a tumor suppressor gene called Menin. MEN-1 is associated with tumors involving the parathyroid glands, anterior hypophysis, and pancreatic islet cells. Primary hyperparathyroidism (PHPT) is the most common feature of MEN-1. In this study, we aimed to evaluate the frequency of MEN-1 associated mutation in patients with PHPT.
Materials and methods
We scanned the medical records of 361 patients with PHPT who were followed-up in our department between January 2010-December 2017. We presented the data of 14 patients who had genetic analysis due to suspicious clinical findings.
Results
Totally 14 patients (two men, 12 women; median age 31.2$\pm$5.7 years) with PHPT were evaluated in genetic analysis. Menin gene mutation was found in 3 (21.4%) patients. In overall patients with PHPT ($n=361$),frequency of MEN-1 ($n=3$) was evaluated as 0.83%. Genetic analysis of three patients with menin mutation were as follows:
Case 1
A 37-year-old man presented with a history of recurrent nephrolithiasis during 14 years. He was diagnosed as PHPT after biochemical analysis. Genetic analysis was reported as MEN-1:c.643_646delACAG (p.Thr215Serfs*13) heterozygous. Other tumoral components of MEN-1 were not found in physical and laboratory examinations.
Case 2
A 35-year-old man was diagnosed as PHPT and prolactinoma. Genetic analysis was reported as MEN-1: c.654+1G>A heterozygous. He did not have other MEN-1 associated tumors.
Case 3
A 26-year-old woman who had hypoglycemia, hyperammonemia, hyperinsulism, partial empty sella and hyperprolactinemia in her medical history was evaluated. Genetic analysis was associated with heterozygous genomic changes as c984c>a in MEN-1 gene on 7th exon.

Conclusion
MEN-1 frequency in PHPT patients is estimated as 1–18%. The diagnosis of PHPT is usually made in second decade in MEN-1 patients. So, the guidelines mostly recommend scanning for PHPT before 30 years of age. In our study population, two patients are between ages of 30 and 40 years. It must be kept in mind that the estimated penetrance of 100% is present up to 40–50 years of age in an individual harboring the MEN-1 gene.

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Cardiovascular Endocrinology and Lipid Metabolism

P624

Impact of the metabolic syndrome on the renal function after partial nephrectomy for nonmetastatic localized renal cell carcinoma

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Introduction and objectives
The most important risk factors of chronic kidney disease (CKD) are diabetes and hypertension. In addition, obesity and metabolic syndrome (MetS) are independent predictive factors of CKD. The objective of our study was to investigate if MetS affects renal function of patients who underwent partial nephrectomy for localized renal cell carcinoma (RCC).
Patients and methods
50 cases of T1N0M0 RCC patients who underwent partial nephrectomy between 2002 and 2016 at our institution were reviewed retrospectively. Patient's history and clinicopathological characteristics of RCC were compared with and without MetS status. Estimated glomerular filtration (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. We evaluated preoperative and postoperative eGFR, as well as overall survival (OS) with MetS status. Data was analyzed using two-sample Student's *t*-tests and the Pearson's χ^2-test (categorical variables). Survival analysis was estimated using kaplan-Meier method comparing with MetS status.
Results
Gender and age had not a statistically-significant impact in patients with and without MetS. ($P>0.05$). Clinicopathological characteristics of RCC were not different in both groups ($P>0.05$). In MetS(+), preoperative and postoperative eGFR were lower than MetS(−) (70.2 ± 25.44 vs 78.6 ± 26.17; 57.3 ± 24.6 vs 71.6 ± 28.1). The difference between preoperative and postoperative eGFR was statistically different between the two groups ($P=0.04$).Overall survival stratified with MetS status wasn't statistically different ($P>0.05$).
Conclusion
Although preoperative and postoperative eGFR are lower in MetS(+) and the changes of eGFR are different between the two groups after partial nephrectomy, MetSdid does not affect overall survival.

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P625

Is SFRP-4 an early potential biomarker related to diabetes and hypertension, in patients with androgenic alopecia?

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Androgenic alopecia (AGA) is an important clinical issue that can cause significant cosmetic problems. Many factors such as genetic, androgen hormones, environmental factors, and inflammation are involved in the pathogenesis of androgenic alopecia. Insulin and insulin resistance have been found increased in individuals with AGA. There are many proinflammatory substances which are playing role in the pathogenesis of androgenic alopecia. Secreted frizzled related protein-4 (SFRP-4) serves as the regulator of insulin exocytosis in pancreatic islet cells. Recently reports have been shown that SFRP-4 serum levels were correlated with insulin resistance and type 2 diabetes mellitus. In two small but notable cohort studies, presuming that SFRP-4 might be an early diabetic indicator, SFRP-4 was observed to increase in serum a few years before the diagnosis of diabetes. In this study, it is aimed to determine the levels of SFRP-4 in androgenic alopecia. Forty-one male patients aged 25–45 years with the complaint of male pattern hair loss which is started before 30 years old and 40 male patients without alopecia were involved to the study. The androgenic alopecia types of patients were determined according to the Hamilton-Norward classification. Specific enzyme-linked immunosorbent assay kits were used for serum SFRP-4 measurement. Ambulatory blood pressure measurements were performed to all participants with an oscillometric type Mobil O Graph NG instrument. The age, BMI and smoking rates were not significantly different between two groups ($P>0.05$). In the group with androgenic alopecia, the SFRP-4 median was 1.50 ng/ml (normal: 0.01–21.20) while in the control group it was 0.57 ng/ml (0.04–5.20) ($P=0.025$). Ambulatory blood pressure measurements were not different between the two groups ($P>0.05$). Spearman's correlation test showed a significantly positive correlation between SFRP-4 and HOMA-IR, sensitive CRP, BMI, and night pulse rate (respectively: rho$=0.265$, $P=0.017$; $\rho=0.274$, $P=0.013$; $\rho=0.220$, $P=0.049$; $\rho=0.226$, $P=0.042$), and a mild negative correlation with HDL-cholesterol values in the AGA group ($\rho=-0.242$, $P=0.030$). In many studies serum SFRP-4 levels were higher in patients with diabetes. We also found that SFRP-4 levels were significantly correlated with BMI, HOMA-IR levels at early ages in men with androgenic alopecia in our study. SFRP-4 may play an important role in the pathogenesis of androgenic alopecia, which could be an early indicator of insulin resistance, diabetes and hypertension that may develop in later ages of these subjects.

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P626

Multi-hormonal deficits in heart failure with preserved ejection Fraction: prevalence and impact on diastolic dysfunction

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Background
In heart failure with reduced ejection fraction (HFrEF), catabolic mechanisms have a strong negative impact on morbidity and mortality. The relationship between anabolic hormonal deficit, thyroid function and heart failure with preserved ejection fraction (HFpEF) has still been poorly investigated. For this reason, we tried to define the prevalence of multi-hormonal deficiencies in HFpEF patients and the relationships between hormonal deficits and echocardiographic indexes.
Materials and methods
40 patients, 27 men and 13 women, aged 59–92 years, were enrolled. Mean BMI was 28.22 ± 4.96 kg/mq. Thirty-six patients showed a moderate degree of diastolic dysfunction (90%) and four patients a mild grade one (10%). Twenty-nine patients (72.5%) were in NYHA III functional class, eleven in NYHA II functional class (27.5%). After an overnight fast, a basal sample was collected for evaluation of N-terminal pro-brain natriuretic peptide, fasting glucose, thyroid-stimulating hormone, free triiodothyronine, free thyroxine, insulin-like growth

factor-1, dehydroepiandrosterone-sulfate, total testosterone (only in male subjects). An echocardiography evaluation was performed.
Results
Only one patient (2.5%) did not exhibit hormonal deficit, eight patients (20%) had deficit of one hormone, 18 patients (45%) of two axes, 12 patients (30%) of three axes, one patient (2.5%) of all four axes. Among them: 97.5% had DHEAS deficiency, 67.5% IGF-1 deficiency, 37% testosterone deficiency, 22.5% a 'Low-T3 syndrome', 20% subclinical hypothyroidism. Patients with IGF-1 deficit showed higher values of left atrial volume, of systolic pulmonary artery pressure (SPAP), of tricuspidal peak velocity (TPV), and lower values of tricuspid annular plane systolic excursion (TAPSE) and TAPSE/SPAP ratio. Patients with testosterone deficiency had higher SPAP and TPV; patients with low T3 syndrome had higher value of right ventricular mid cavity diameter. Hormonal dysfunction was independent from the presence of comorbidities, and there was no difference between male and female subjects.
Conclusions
Multi-hormonal deficits are associated with right ventricular dysfunction and diastolic dysfunction in patients with HFpEF. Therefore they can be considered as an independent factor negatively influencing natural history of the syndrome.

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P627

Cross-hormone treatment: review of cardiovascular risk factors and bone mineral density in 25 transsexual subjects followed in a tertiary hospital

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Introduction and objectives
Transsexuality refers to discrepancy between the assigned sex/gender at birth and the one that the subject identifies with. The use of the cross hormone treatment as sex/gender change method implies the necessity of monitorize the hormone levels and potential treatment risks. Our study tries to evaluate the relationship between the hormone changes and the changes in the cardiovascular risk factors and the bone mineral density.
Methods
We conducted a retrospective analysis of 25 transsexual subjects (nine transsexual women (36%) and 16 transsexual men (64%)) receiving cross hormone treatment for 24 months and monitoring in Hospital Clínico San Carlos. Demographic information, cardiovascular risk factors and bone mineral data were collected.
Results
25 patients were evaluated with a mean of age of 37.8 ± 10.3 for transsexual women and 34.13 ± 10.6 for transsexual men ($P = 0.39$). 33% of transsexual women and 13% of men were smokers ($P < 0.01$). Mean of spine T-score for transsexual women was 1.06 ± 0.18 and 0.83 ± 0.33 for men ($P < 0.05$). No other cardiovascular risk factors were found nor differences between both groups. During the 24 month follow-up, no worsening of cardiovascular risk factors was found in both groups. According to the transsexual women it was found a significant reduction in systolic blood pressure (SBP) (117 mmHg $\pm$ 9.12 mmHg vs 112.2 mmHg $\pm$ 12.1 mmHg ($P = 0.04$)). On the other hand, it was identified a positive correlation between testosterone levels and first, total cholesterol ($r = 0.69$, $P < 0.04$) and second, LDL-c ($r = 0.73$, $P < 0.02$), showing that the higher testosterone levels, the higher cholesterol ones. No differences in terms of bone mineral density were found in any of the groups.
Conclusions
According to our results, the cross hormone treatment is safe in terms of no worsening cardiovascular risk factors and bone mineral density. In order to avoid long term worsening in both aspects it is very important to maintain de estradiol and testosterone levels in the correct range and try to look carefully the cardiovascular risk factors.

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P628

How the diagnose of the dilatation of ascending aorta in Turner syndrome can be verified?

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Introduction
Two major strategies can be used to verify the diagnosis of ascending aortic dilatation in Turner syndrome (TS): the diameter of the aorta adjusted for body surface area (BSA) can be estimated or the ratio of the ascending/descending aorta may be assessed.
Aim
To identify the difference of the prevalence of ascending aortic dilatation in patients with Turner syndrome by measuring the diameter of the ascending aorta adjusted for BSA and by estimating the ratio of ascending/descending diameter of aorta (AD/DD).
Methods
63 women with TS (45, X 68%) treated in the Hospital of Lithuanian University of Health Sciences were the subjects of the study. Seven of the patients were excluded from the study as MRI angiography was contraindicative. 56 females with TS $\geq$18 yrs (mean age 30.98 ± 9.1 yrs) underwent MRI angiography using Gadolinium based contrast media. Diameters of the ascending aorta were evaluated in three positions: in the level of the aortic sinuses (D1), in sinotubular junction (D2) and in the inferior margin of the right pulmonary artery (D3). The largest diameter of the aorta was included in the analysis. The diameter of descending aorta was measured between the left pulmonary artery and the superior part of the left atrium (D4). Aortic dilatation was considered to be present if the larger diameter of ascending aorta (AA) was ≥ 2 cm/m^2 (BSA-normalized) and/or the ascending and the descending ratio (AD/DD ratio) was ≥ 1.5.
Results
Out of 56 studied women, 48% ($n = 27$) had the diameter of the ascending aorta ≥ 2 cm/m^2, 32.14% ($n = 18$) had aortic dilatation confirmed after calculating the AD/DD ratio ($\geq$ 1.5). No significant difference was found ($P = 0.057$). If the dilatation of the ascending aorta was present the measurements of the ascending aorta were larger in all positions (D1 17.07 mm/m^2 vs. 22.8 mm/m^2, $P < 0.001$; D2 14 mm/m^2 vs 17.6, $P < 0.001$; D3 15.26 mm/m^2 vs 19.49 mm/m^2). The size of the aorta correlated with age in all positions (D1 $r = 0.362$, $P = 0.006$; D2 $r = 0.336$, $P = 0.011$; D3 $r = 0.381$, $P = 0.004$; D4 $r = 0.484$, $P < 0.001$).
Conclusion
Measuring the diameter of ascending aorta adjusted for BSA or calculating the ratio of the ascending/descending aorta can verify the existence of aortic dilatation equivalently in Turner syndrome.

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P629

Fibroblast growth factor-21 predicts adverse outcome in community-acquired pneumonia

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Introduction
Fibroblast growth factor-21 (FGF-21) is a recently discovered hormone acting as a central regulator of metabolism via adaptation of glucose homeostasis, insulin sensitivity, and ketogenesis. While acute systemic inflammatory conditions come along with profound alterations of metabolism, the role of FGF-21 in these acute phase responses is still unknown.
Methods
This is a secondary analysis of two randomized, controlled trials in patients presenting to the emergency department with community-acquired pneumonia. Multivariate regression models were performed to analyze associations of FGF-21 with disease severity, mortality, length of hospital stay and duration of antibiotic treatment.
Results
A total of 509 patients were included in the analysis, 150 patients from the ProCAP trial and 359 from the STEP trial. Serum FGF-21 on admission was significantly correlated to disease severity as measured by pneumonia severity index ($R^2=0.159$, $P<0.0001$). FGF-21 levels at admission were associated with reduced likelihood of clinical stability, adjusted hazard ratio (HR) 0.88 (95% CI, 0.81–0.96; $P=0.006$) and consecutively prolonged duration of intravenous antibiotic therapy (adjusted HR 0.56; 95% CI, 0.15–0.97; $P=0.008$). FGF-21 levels were higher at admission in nonsurvivors than in survivors (median 1307.6 vs 416.7 pg/ml; $P<0.001$), yielding a 1.41-fold increased adjusted odds ratio of 30-day mortality (95% CI, 1.05–1.90; $P=0.02$). FGF-21 was found to identify patients for 30-day mortality with superior discriminative power (AUC 0.74) compared to procalcitonin (AUC 0.62) or c-reactive protein (AUC 0.48).
Discussion
FGF-21 was markedly increased in patients with community-acquired pneumonia and was found to identify patients at risk for adverse outcome more effectively than routine diagnostic markers.

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Clinical case reports - Pituitary/Adrenal

P630

Low dose duloxetine and the risk of hyponatraemia

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Duloxetine is a serotonin/norepinephrine reuptake inhibitor, prescribed frequently as a first line treatment for Diabetic neuropathy. It is also prescribed for treatment of depression, anxiety disorder and chronic musculoskeletal pain. Hyponatremia is a known adverse effect of most SSRIs including duloxetine and can potentially be life-threatening.Duloxetine induced hyponatremia, however, is relatively rare specially on low doses and is typically seen in the elderly frail patients. We report a case of duloxetine-induced hyponatremia in a 76 year old lady with a background of type 2 diabetes mellitus, hypertrophic obstructive cardiomyopathy, orthostatic hypotension and gradual functional decline and increased frailty. Initially on Fludricortisone and Midodrine for orthostatic hypotension, she was started on Duloxetine by her family doctor for neuropathic pain a week prior to presentation. She was not on diuretics. She then presented to the A&E with frontal headache, confusion, disoreintation and recurrent vomiting. Laboratory findings revealed hyponatremia, low serum and raised urine osmolalities, and increased urine sodium. Her TSH and Cortisol levels were normal. Syndrome of inappropriate antidiuretic hormone was considered and, duloxetine was discontinued. She was treated with fluid restriction, and required intravenous sodium chloride administeration due to hypotension. She responded well to treatment and her confusion and vomiting were improved after correction of sodium. Health care practitioners in general and diabetologist in specific should be aware of the possibility of duloxetine-induced hyponatremia, particularly in elderly frail patients.Elderly people are vulnerable because fluid levels become more difficult for the body to regulate.Close laboratory monitoring is essential after initiation of treatment.

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P631

Endocrine disorders in a patient affected by MELAS syndrome: a case study

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Introduction
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, combined together, under the name of MELAS syndrome, constitute one of the mitochondrial genetic diseases with dominant progressive neurodegenerative symptoms. Although nervous system involvement is often the first manifestation of the disease, during the course of the disorder, patient can develop a wide spectrum of endocrine disorders ranging from GH deficiency and hypoparathyroidism to diabetes.
Case study
19-year old patient with MELAS syndrome was admitted to the Department of Endocrinology for routine check-up and evaluation of carbohydrate metabolism. He presented with standard features of the symptom like: encephalopathy, myopathy, hearing impairment, mental retardation, vision disturbances and history of seizures and stroke-like episodes. During the course of the disease he developed numerous endocrine manifestations of this mitochondrial pathology. He was diagnosed with short stature due to GH deficiency, after that, based on decreased calcium and PTH levels, hypoparathyroidism was recognized and suplementation was introduced. Later he was diagnosed with secondary adrenal insufficiency requiring hydrocortisone replacement therapy. During evaluation of delayed puberty hypogonadotropic hypogonadism was identified. Additionally the review of medical history revealed recurring episodes of hyponatremia probably due to unrecognized SIADH syndrome. During current hospital stay we evaluated the carbohydrate metabolism ruling out mitochondrial diabetes. Fasting glucose was within normal limits and HbA1c level was at 5.4%. Further diagnostic unmasked concomitant insulin resistance with HOMA-IR at 3.3. The dose of hydrocortisone was adjusted and the patient was referred to endocrine outpatient clinic for regular follow-up.
Conclusions
Endocrine dysfunctions, with many of them occurring concomitantly, complicating the course of the disease, are an important aspect of mitochondrial diseases, especially in patients with MELAS. Mitochondrial diabetes is hypothesized to occur as a result of insulin deficiency rather than insulin resistance, however, in some patients, the second mechanism may also play a crucial role

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Clinical case reports – Thyroid/Others

P632

Patient with neurofibromatosis type 1 and follicular thyroid cancer

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Objectives
Neurofibromatosis type 1 (NF1) is an autosomal, dominant, genetic disorder. The genetic lesion in neurofibromatosis type 1 is located at locus 17q11.2 that harbors the neurofibromin gene. Patients have 3-4 times higher possibility to develop malignancies relative to the general population. The endocrine manifestations of neurofibromatosis include precocious puberty, short stature, osteoporosis and pheochromocytoma. We present a patient with neurofibromatosis type 1 and thyroid carcinoma.
Methods
A 46-years-old female patient unterwent total thyreoidectomy for multinodular goiter. Pathology report revealed a macrofollicular variant of follicular thyroid

carcinoma, 4 cm in maximum diameter ($T_2N_0M_0$). The patient reveived radioactive iodine (^{131}I) therapy 70 mCi and L-thyroxine suppression therapy. From the medical history the patient reported a brain tumor surgery, at the left brain lobe, at the age of 4 years, which resulted in left facial nerve palsy. She also had delayed puberty.
Results
From the clinical examination the patient had typical signs of NF1 such as café au lait spots, subcutaneous neurofibromas, axillary freckles, as well as hamartomas of the iris (Lisch nodules) and low stature. In the family history there were no family members with NF-1 reported. The patient fulfilled the 4 out of 7 diagnostic criteria of NF-1. Brain MRI reported gliotic lesions in the hypoplastic left lobe and the cerebellum. The biopsy of a skin nodule revealed neurofibroma, whereas further diagnostic examinations for pheochromocytoma and osteoporosis were negative.
Conclusion
Clinical diagnosis requires the presence of at least 2 of the 7 criteria to confirm the presence of NF1. Many of these signs do not appear until later childhood or adolescence and the diagnosis often is delayed, despite suspicious features for NF1. Although rare, the coexistence of thyroid cancer is possible and should be evaluated

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P633

A rare mediastinal signet-ring cell carcinoma revealed after postpartum thyroiditis – a coincidence or a link?

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Introduction
Postpartum thyroiditis is an autoimmune process that occurs in 5% of the women, precipitated by immunological rebound. The majority off signet-ring cell carcinoma (SRCC) tumors arise from the stomach, colon and breast, malignant transformation of a bronchogenic cysts being exceptionally.
Aim
We present a case of a rare mediastinal SRCC of the mediastinum, diagnosed initially with a postpartum thyroiditis.
Case presentation
A 34 years old woman presented with complains of neck and anterior thoracic discomfort, agitation, palpitation, 3 months after getting birth. The initial workup found thyrotoxicosis, with high level of thyroid antibodies and autoimmune pattern at ultrasonography, with reduced uptake of Tc-99m pertechnetate at thyroid scintigraphy. Thyrotoxicosis remission, after 2 months of evolution, revealed a superior cava vein syndrome. Chest radiography showed a large mediastinum and cystic-tumor in CT. She associated pericardial effusion, without hemodynamic significance. In spite of sophisticated diagnostic workup, detailed investigations fail to reveal other site implicated at the moment. The tumor resection was complicated with metastatic involvement of the pleura with massive pleural effusion, rising level of the pericardial fluid with carcinomatous signet-ring cells, poor response to treatment and breast metastasis later on. The histopathology and immunohistochemistry of mediastinal mass and breast nodule concluded that it is the case of a very rare mediastinal bronchogenic cyst with malignant transformation in a SRCC. The overall progression was poor with the patient's death 1 year after diagnosis.
Conclusion
There are limited data about evolution of bronchogenic cysts or SRCC in pregnancy or postpartum and how endogenous estrogens influences tumor's grow. The malignant transformation of a bronchogenic cyst happens exceptionally. We know that postpartum thyroiditis is precipitated by immunological rebound that follows the partial immunosuppression of pregnancy and malignancy is also an immunosuppressive state, so the association of postpartum thyroiditis in this conditions is uncommon.

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P634

When it is the time of prophylactic thyroidectomy to children with medullary thyroid cancer with RET proto-oncogene Cys634Trp mutation in a family with multiple endocrine neoplasia type 2A

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Background
Almost all patients with Multiple Endocrine Neoplasia, type 2A (MEN 2A) have MTC. C-cell hyperplasia develops early in life and can be viewed as the precursor lesion for MTC. Children with MEN2A who have a total early thyroidectomy have an excellent chance of remaining disease-free.
Objectives
To follow-up the children with RET mutation in a family with MEN2A.
Methods
We report a family with MEN2A in which the first patient had bilateral pheochromocytoma associated with MTC. Molecular genetic testing of the RET exon confirmed the mutation at codon 634(Cys634Trp) in RET exon 11.We screened all her family members; six had the same RET proto-oncogene mutation; four females and two children. A boy had normal level of calcitonin (identiphied with RET mutation at two months), his mother developed MTC during pregnancy. The second boy-ten years old had high level of calcitonin; his mother had MTC and bilateral pheochromocytoma. Monitoring the children to every 6 months: physical neck examination and neck ultrasound, blood tests of calcitonin and CEA.
Results
In our group, the boy who was diagnosed at 2 months with RET mutation has been prophylactic thyroidectomies at 7 years. He presented two areas of C-cell hyperplasia. The second boy who now has 17 years has high values of calcitonin and CEA, and parents refuse the surgical excision.
Conclusion
At the child presented by us, parents delaying the agreement for thyroidectomy, and this could result in the development of the MTC.

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P635

Subacute thyroiditis in association with psoriasis and behcet's disease

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Introduction
Subacute thyroiditis is usually a self-limited pathology, possibly of viral aetiology, defined by cervical pain and sometimes systemic symptoms. Its association with autoimmune diseases doesn't seem to be more frequent than in the general population.
Clinical case
Clinical findings of thyrotoxicosis with 3 weeks of evolution associated with anterior cervical pain and fever up to 38 °C. The patient presented with recurrent mouth sores since childhood and vaginal sores in the prior year. She also presented with hand nail *pitting* and onycholysis in the former 4 years. The maternal aunt had thyroid cancer and two maternal cousins had multinodular goitre. No family history of autoimmune diseases. The thyroid ultrasound revealed an enlarged lobulated gland with hypoechoic areas. Periodic analytical study was conducted (in 2^{nd}/ 4^{th}/ 9^{th}/ 15^{th} weeks): TSH – 0,024/ <0,01/ 32,139/ 4,69 µUI/ mL (0,35–4,94); free T3 – 5,33/ 3,27/ 2,81/ 3,19 pg/ mL (1,71–3,71); free T4 – 2,39/ 1,28/ 0,62/ 0,88 ng/ dL (0,70–1,48); C reactive protein – 66,80/ 27/ 0,4/ 0,2 mg/ L (<0,5); anti-thyroid antibodies were negative. Eight months after the beginning of the symptoms, TSH was of 0,894 µUI/ mL. The patient was initially treated with propanolol 20 mg every 8 hours and ibuprofen 400 mg every 8 hours. In this period she referred worsening of the mouth sores. In subsequent consultations the dose of beta-blocker was progressively diminished until its suspension after 2 months. A progressive improvement of the pain symptoms took place with complete disappearance after 6 months. The patient was at the same time observed by the Dermatology speciality which diagnosed nail psoriasis. Despite a period of clear, short, analytical hypothyroidism, it was decided not to initiate levothyroxine given the absence of symptoms related to it. In the beginning of 2017 the patient was observed in the autoimmune diseases

consultation were she was diagnosed with Behçet's Disease. From the undertaken study, it stands out the positivity for HLA-B*35 and HLA-A*02 antigens.
Conclusions
Subacute thyroiditis usually presents a self-limited, typical evolution, and remits without leaving sequelae. In the presented case it was possible to document that particular evolutional pattern, even in the context of significative analytical hypothyroidism. Within our knowledge, the association between Subacute Thyroiditis, Behçet's Disease and Psoriasis has never been reported. In the first, it is documented an increase in prevalence of antigen HLA-B*35, and in the last two of the antigen HLA-A*02.

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P636

Primary haemoglobinopathies as a cause of secondary endocrinopathies

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Background
Haemoglobinopathies are inherited disorders of haemoglobin that predispose to endocrinopathies. The common ones include growth delay, hypogonadism and subsequent osteopaenia. Less commonly seen are diabetes mellitus, thyroid and adrenal disorders. Aetiology is multifactorial and includes tissue hypoxia, chronic anaemia, iron overload, high energy demand, genetic influence and malnourishment. We present three case reports which illustrate the endocrinopathies amongst patients with thalassaemia and sickle cell disease.
Cases
A 27 year old, transfusion dependent, lady with sickle cell disease presented with amenorrhoea for 5 years. She had a normal menarche. She was previously on a combined contraceptive pill and was having menstrual periods. Since stopping, she has noticed complete amenorrhoea. She denied galactorrhoea, headache or visual disturbance. Her hormonal profile showed low levels of luteinising hormone (LH), 0.9iU/L and oestradiol (E2) <70 pmol/L.Prolactin was normal. MR pituitary was unremarkable. Bone density scan (DEXA) showed osteopaenia. She was referred to another hospital with haemoglobinopathy service for joint fertility management. A 50 year old lady with transfusion dependant beta thalassaemia major had diabetes mellitus, osteoporosis and premature ovarian failure. She is currently on novorapid, lantus, deferasirox and penicillin v. Hormonal profile showed low levels of LH, follicular stimulating hormone (FSH) and E2. DEXA scan was in keeping with osteoporosis (lumbar spine T score of -3). Her diabetes and premature ovarian failure are secondary to transfusion related haemosiderosis. She was referred to joint fertility clinic and successfully delivered her first baby at the age of 33 after in-vitro fertilisation and is now on continuous femoston and osteoporosis treatment. She has regular follow ups with an endocrinologist. A 27 year old beta thalassaemia major sufferer presented with growth delay, amenorrhoea and osteoporosis as a consequence of transfusion related iron overload. She was referred to paediatrics endocrinology earlier on due to her growth delay. She was on growth hormone until the age of 20. Menarche was normal. She was started on HRT for premature ovarian failure. Recognition of endocrine disturbance is of utmost importance in the follow up of haemoglobinopathies. Hormone replacement therapy plays an important role in treatment and ensuring adequate quality of life in these patients. They should be routinely screened for osteoporosis. In females, establishment of desire for pregnancy should be done earlier on as they may require assistance with fertility which are best cared for in a multidisciplinary team setting.

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Developmental endocrinology

P637

Effect of desacyl ghrelin on protein expression of GHS-R1 receptor in human placental cells

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Introduction
Ghrelin is an orexigenic hormone with two isoforms: Acyl Ghrelin (AG) and Desacyl Ghrelin (DAG). AG binds to its specific receptor GHS-R1 and stimulates growth hormone secretion. DAG also binds to GHS-R1 receptor, but with 1000 times less affinity than AG. Effect of DAG on cell proliferation and inhibition of apoptosis has been reported. However, there are no studies of DAG function in human placenta. For first time, this work analyzed the effect of DAG on viability, proliferation and protein expression of GHS-R1 of human placenta cells.
Objective
To evaluate the effect of DAG on viability, proliferation and protein expression of GHS-R1 receptor in human placental cells line BeWo.
Materials and methods
BeWo cells were cultured in F-12K medium and incubated for 72 h at 37 °C and 5% CO2. First, BeWo cells were incubated for 24 h. Then, cells were treated with 3nM DAG for 12, 24, 48 and 72 h for viability assay and 24 h in the case of cell proliferation assay. To evaluate protein expression of GHS-R1 receptor, cellular homogenates were analyzed by Western Blot using anti-GHS-R1 (1:1000) as first antibody by 20 h and anti-mouse (1:22500) as secondary antibody by 2 h. Results were analyzed by ANOVA; $p \leq 0.05$ was considered as significant.
Results
Cells treated with DAG did not show differences in cellular viability ($P>0.05$) compared against control cells at all times examined. Similarly, proliferation of cells treated with DAG was not different ($P>0.05$) from control cells at 24 h. GHS-R1 protein expression of cells treated with DAG increased 42% at 12 h ($P=0.029$) and 36% at 24 h ($P=0.025$). However, GHS-R1 protein expression decreased 35% at 48 h ($P=0.005$) compared with control cells.
Conclusions
DAG has no effect on viability and proliferation of human placental cytotrophoblast cells. However, DAG induces changes in protein expression of GHS-R1 receptor, suggesting that could induce signals downstream of this receptor, on sensors or nutrient transporters.

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Diabetes (to include epidemiology, pathophysiology)

P638

Short-term impact of the 2017 diabetes awareness day in Greece

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Introduction/Aim
Disease awareness days are numerous and varied [1]. In the present study we tried to assess the short-term impact of the 2017 diabetes awareness day in Greece by examining localized relevant internet-based searches.
Materials/Methods
We collected data from Google Trends™ regarding relative [internet] search volumes (RSVs) with key words "diabetes" (in Greek and English; study group) and "breast cancer" (also in Greek and English; control group). We collected only data from Greece from the seventh day preceding Diabetes Awareness Day (DAD; November 14, 2017) and Breast Cancer Awareness Day (BCAD; October 25, 2017) till the seventh day following these days. Comparisons of RSVs of the days preceding and following DAD and BCAD were done with the Wilcoxon paired test and the Sign test (statistical significance was set at $P<0.05$).
Results
There were significantly more RSVs for diabetes than breast cancer ($P=0.001$, Wilcoxon test) and significantly more RSVs in the days preceding than the days following DAD or BCAD ($P=0.016$, Sign test).
Discussion/Conclusion
Diabetes was interestingly more popular in internet searches than breast cancer. Apparently diabetes is more diversified as a search term than breast cancer (a lot of its internet searches concern diet, recipes and lifestyle modifications) and this may - partially - explain its predominance. However, more RSVs were noted before than after DDF or BCAD; this finding may indicate a lower than anticipated effectiveness of these disease awareness days and lends credence to their critics [2].
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P639

Optimization of the use of outpatient diabetes center through a coordinated task force between primary care and endocrinology unit

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Objetives
To analyze the profile of patients referred from Primary Care (PC) to Outpatient Diabetes Center (ODC), as well as the evolution of self-assessment measured by Chronic Care Model IEMAC (Instrument for the Evaluation of Attention Chronicity Models) tool after implementation of a coordinated Task Force between Primary Care and Endocrinology Unit.
Methods
The working group of the Advanced Diabetes Center in Cádiz-San Fernando Sanitary Area was constituted in 2014, with health professionals of different profiles and care's level (one primary care physician from each of the 10 Health Centers of the area, 4 primary care nurses, 5 endocrinologists and 2 endocrinology nurses) The initial self-assessment was made by using IEMAC-Diabetes tool. A value proposal was developed with priority areas of intervention, aimed primarily to propagate Outpatient Diabetes Center's service portfolio and thus optimizing its use. The data of patients referred to ODC were analyzed from April 2015 to December 2016.
Results
A total of 295 patients were derived to ODC (aged 63.03 ± 16.3 years) with HbA1c of 8.54%. The association with other cardiovascular risk factors was 66% hypertension, 56.6% dyslipidemia and 57.8% excess weight. The rate of micro and macrovascular complications was 46.6% and 44.4% respectively. After one year follow up, a significant HbA1c reduction was observed. In 2015, only 40% fulfilled criteria included in the agreed Outpatient Diabetes Center's portfolio and in 2016 amounted to 76%. The most common reason for referral was diabetic foot (37%). Of these, 24% required minor amputation and 9% greater. The self-assessment over attention of patients with diabetes, evaluated through IEMAC among the professionals of the task force, improved from an overall score of 32/100 initially to 55/100 after two years.
Conclusions
After implementation of a coordinated task force group between Primary Care and Endocrinology Unit in Puerta del Mar Hospital, the adequacy in the referral to Outpatient Diabetes Center has improved significantly, with an increase in the score of the self-assessment on attention to patients with diabetes in the area.

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P640

The 4-hydroxynonenal mediated oxidative damage of blood proteins and lipids involves secondary lipid peroxidation reactions

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Lipid peroxidation is linked with several metabolic diseases. Lipid peroxidation causes cellular damage through reactive aldehyde species such as 4-hydroxyonenal (4-HNE). The exact mechanism(s) by which 4-HNE causes damage in the intravascular compartment is not exactly known. Using an *in vitro* system, we investigated the damage induced by 4-HNE on the blood by measuring protein carbonyl groups and thiobarbituric acid reactive substances (TBARS) following 4-HNE treatment. We showed that treatment with 4-HNE increased the carbonylation of proteins and the formation of TBARS in the blood plasma. We also tested whether phenelzine, a scavenger of aldehyde species, or U-83836E, a scavenger of lipid peroxy radicals, attenuates the damage caused by 4-HNE. We showed that phenelzine or U-83836E can both mitigate the effects of 4-HNE on the proteins and the lipids of the blood plasma. We explained the above results through a model that involves secondary lipid peroxidation reactions initiated by 4-HNE.

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Effect of duration of exposure to glucose-based peritoneal dialysis fluid on peritoneal membrane thickness

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The efficacy of peritoneal dialysis (PD) is closely related to the status of the peritoneum. Long-term PD leads to structural and functional changes in the peritoneum and affects dialysis adequacy. Also high-glucose content of dialysate accelerates peritoneal fibrosis. It is reported that ultrasonography (USG) reflects parietal peritoneal membrane thickness and PD duration is related with peritoneal thickness. This study aimed to evaluate peritoneal thickness with USG in PD patients.
Method
A total 20 adult PD patients (mean age 48.8 ± 3.8 years, 65% female) were included in the study. The patients used continuous ambulatory ($n = 14$) or automated ($n = 6$) PD regimen with 1.36%, 2.27% and 3.86% glucose based solutions. Patients were divided into two groups according to PD treatment durations: shorter than 60 months (Group 1, 34.6 ± 4.8 months, n = 10) and longer than 60 months (Group 2, 110.9 ± 8.6 months, $n = 10$). Dialysis adequacy (D/P creatinine, pKT/V, creatinine clearance) and parietal peritoneum thickness of two groups were measured.
Results
The mean ages, gender distributions, body mass indexes and PD types of both groups were comparable. There was no statistically significant difference between D/P creatinine, pKT/V and creatinine clearance values of the two groups at the initial and last visits. The final ultrafiltration amount was significantly higher (1269 ± 496 vs. 847 ± 344 mL, $P = 0.034$) and the residual urine volume was significantly lower (275 ± 544 vs. 799 ± 525 mL, $P = 0.016$) in group 2. In all patients, the creatinine clearance and the amount of residual urine significantly decreased, and the amount of ultrafiltration increased over time ($P < 0.001$). There was no significant difference in creatinine clearance, ultrafiltration amount and residual urine volume percent changes between the two groups. Parietal peritoneum thickness values of group 1 and 2 were similar in the right upper (0.38 ± 0.11 vs. 0.40 ± 0.06 mm), left upper (0.40 ± 0.07 vs. 0.41 ± 0.11 mm), right lower (0.42 ± 0.11 vs. 0.41 ± 0.11 mm) and left lower (0.42 ± 0.11 vs. 0.41 ± 0.09 mm) zones, respectively ($P > 0.05$).
Conclusion
As the duration of PD treatment increases, the peritoneal structure changes. We did not find out any difference in peritoneal thickness between the groups according to PD duration. We found a decrease in PD efficacy over time with glucose based solutions in different concentrations, but this decrease was not related to the duration of the treatment.

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P642

Coexistence of mitochondrial diabetes and primary amyloidosis

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Introduction
Primary amyloidosis is a multi-systemic disease difficult to identify given the diversity of the disorders that it can cause especially at an early stage of the disease. This makes its diagnosis difficult in case of association with a pathology that can be intricate with its clinical expression. In this context we report the first case in the literature associating mitochondrial diabetes (DM) with a primary amyloidosis
Case
A 32 years old girl, with family history of diabetes and maternal transmission, refer to our service for diabetes of primo discovery revealed by a frank hyperglycaemia without ketosis. The negativity of anti-beta cell antibodies and the presence of extra-pancreatic manifestations at type of bilateral perception deafness, sensitivomotor neuropathy, glomerular nephropathy and the presence of jagged red fibers characteristic of mitochondrial cytopathy on muscle biopsy, led

us to retain the diagnosis of a DM. The biomolecular study then confirmed the mutation most frequently described in the literature: m.3243A > G (tRNA Leu) in the mitochondrial genome. Moreover, in front of the echocardiography appearance of concentric hypertrophic cardiomyopathy, with hyperechoic and brilliant granite appearance, unusual in DM and suggestive of overload cardiomyopathy, a biopsy of the salivary glands was performed and confirming the presence of a primary amyloidosis.

Discussion and conclusion

The association of DM with amyloidosis has never been described in the literature. Such an association may be a prototype of interrelation between the nuclear genome involving genes having a key role in the metabolism of amyloid deposits and the mitochondrial genome thus inducing a vicious circle that can sustain a process of cellular apoptosis induced by an alteration of the dynamism of the intra-mitochondrial respiratory chain already reported *in vitro*. Certainly the progress of molecular biology and a better understanding of signaling signals of intracellular proteins allowing clarifying the etiopathogenic link of such an association.

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Endocrine Disruptors

P643

Role of Pro-inflammatory biomarkers in Graves' disease: A case-control Study

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Introduction

Graves' disease (GD) is one of the commonest organ specific autoimmune thyroid disease. Surgical thyroidectomy is one of the definitive treatment modalities. Autoimmunity has been implicated as one of the main cause of GD. In this context, we set out study the role of Pro- inflammatory cytokines in GD.

Material and methods

This prospective case-control study was conducted on surgically managed GD patients. Institutional ethical committee approval was obtained. Diagnosis of GD was based on clinical picture, thyroid function tests, radionuclide scanning and histopathology. Exclusion criteria were subjects any systemic or chronic inflammatory disease or any medication which interferes with the normal function of the hypothalamic-pituitary-gonadal axis. Serum samples were collected from 32 GD subjects and 30 age matched healthy controls. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF-α) and high sensitive C reactive protein (hsCRP), Leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.

Results

The mean hSCRP level in GD and controls were 16.6 ± 2.1 mg/mL and 5.8 ± 1.1 mg/mL respectively. The mean TNF-α level, IL-6 level and Leptin levels were 256 ± 21 pg/mL, 11.4 ± 3.2 pg/mL and 27.5 ± 4.4 ng/mL respectively. There was statistically significant difference of all the pro-inflammatory cytokines compared to controls (P value < 0.05).

Conclusions

This study shows raised titers of pro-inflammatory markers – IL-6, TNF-α and hsCRP, leptin correlated with GD suggesting a contributory role. But, the exact immuno-modulatory role and pathogenetic mechanism needs active research.

(Key words: Graves' disease, Tumour necrosis factor, Interleukin-6, Goiter, Auto-immunity, Leptin)

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P644

Endoplasmic reticulum stress-mediated apoptosis and cell cycle arrest were caused by resveratrol, a phytoestrogen, in malignant melanoma cells

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Resveratrol, a dietary product present in grapes, vegetables, and berries, is phytoestrogen that regulates signaling pathways that control cell division, and growth, apoptosis, and metastasis. Melanoma, also known as malignant melanoma, is a type of cancer that develops from the pigment-containing cells known as melanocytes. Especially, malignant melanoma is pernicious and proliferates more readily than any other skin cancer. In the present study, we evaluated the anti-cancer effect of resveratrol on melanoma cell proliferation. Treating A375SM cells with resveratrol resulted in a decrease in cell growth. We also examined the alteration of cell cycle-related genes by western blot. Treatment with resveratrol was found to increase the gene expression of p21 and p27 and decrease the gene expression of cyclin B. We confirmed the generation of ROS and ER stress at both the cellular and protein level using a DCF-DA assay, TUNEL assay, and western blot. Resveratrol induced the ROS-p38-p53 pathway by increasing the gene expression of phosphorylated p38 MAPK (p-p38 MAPK) and the p53 and ER stress pathway by increasing the gene expression of phosphorylated eIF2α (p-eIF2α) and CHOP. The enhanced ROS-p38-p53 pathway and ER stress pathway promoted apoptosis by downregulating Bcl-2 expression and upregulating BAX expression. Overall, resveratrol appears to be an inducer of ROS generation and ER stress and can be responsible for growth inhibition and cell cycle arrest of A375SM melanoma cells.

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P645

Endocrine related adverse events associated with immune checkpoint blockade therapy: a retrospective analysis

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Background

Immune checkpoint inhibitors (ICI) have become a clinically validated treatment for numerous types of tumor including melanoma, lung, and kidney carcinoma. These treatments can cause immune-related adverse events affecting several organs including the endocrine system.

Aims

The aim of this study was to characterize the type and the onset of the ICI associated-endocrinopathies.

Materials and methods

This retrospective cohort evaluation included patients with advanced cancer candidate for ICI treatment attending the Oncology Unit at S.Orsola-Malpighi Hospital of Bologna from January2016 to September2017. All patients were treated with a different schedule according to the Authority-approved ICI doses and administration.

Results

Sixty-nine patients were included in this study and they were followed for 32 weeks in average (range 2 to 88 weeks). Fifty-one patients were treated with nivolumab ($n=23$ lung-carcinoma, $n=22$ melanoma, $n=6$ kidney-carcinoma), 12 with pembrolizumab ($n=10$ melanoma, $n=2$ lung-carcinoma), 4 with ipilimumab ($n=2$ kidney carcinoma, $n=2$ melanoma), and 2 with ipilimumab + nivolumab ($n=1$ melanoma, $n=1$ liver-cancer). Among these 69 cases, 10 (14.5%) showed drug-induced endocrinopathies: 1 had a central hypoadrenalism with ipilimumab, 1 had a sudden-onset of diabetes mellitus with nivolumab, and 8 developed thyrotoxicosis with nivolumab ($n=5$), with ipilimumab + nivolumab ($n=2$) and with pembrolizumab ($n=1$). Central hypoadrenalism and diabetes developed at 4th (12 weeks) and at the 26th drug administration (52 weeks), respectively. These subjects required gluco-corticoid and insulin lifelong replacement therapy, respectively. Instead, thyrotoxicosis induced by nivolumab and pembrolizumab occurred at the 3rd drug administration (6-9 weeks), whereas those caused by ipilimumab + nivolumab appeared in one subject at the 3rd (6 weeks) and the other at the 7th drug administration (14 weeks). The average time of thyrotoxicosis was 3 weeks (1-8 weeks). Of these 8 thyrotoxicosis, 4 subjects progressed to overt hypothyroidism ($n=2$ nivolumab, $n=2$ ipilimumab + nivolumab) and 4 to euthyroidism ($n=3$ nivolumab, $n=1$ pembrolizumab). All these subjects had no previous history of thyroid disease. The etiology of the endocrinopathies are presumably immune, however the specific known autoimmunity in selected patients was negative (anti-GAD antibodies for diabetes, and anti-thyroid peroxidase, anti-tireoglobulin, anti-TSH receptors in 2 thyrotoxicosis).

Conclusion
In our clinical records, endocrine related adverse events were relatively common with thyrotoxicosis being the most frequent. All adverse events were successfully managed without needing to stop ICI treatment. These findings suggest that a close interaction between the endocrinologist and oncologist should be advocated for a rapid identification and treatment of ICI-induced endocrinopathies.

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Endocrine tumours and neoplasia

P646

Evolution of endocrine surgery during three consecutive years in a tertiary-care university hospital of Madrid (Spain)

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Introduction
The availability of an increasing therapeutic arsenal for endocrine diseases seems to explain the current trend towards a decrease in the indications of endocrine surgery. However, this trend requires a detailed study before being confirmed in our setting.
Objectives:
We aimed to assess the trends in the performance of endocrine surgery, in children and adults, during three consecutive years (2014, 2015 and 2016) in our University Tertiary-Care Referral Hospital, settled in Madrid (Spain).
Methods
We contacted the Pathology Service and the main surgical Services involved, collected the number of thyroidectomies, parathyroidectomies, adrenalectomies and surgeries in the hypothalamic-pituitary area per year in the period of study, and calculated the corresponding interannual and overall variation rates.
Results
The number of thyroidectomies, parathyroidectomies, adrenalectomies and surgeries of lesions in the hypothalamic-pituitary area performed per year were 264, 57, 30 and 43, respectively, for 2014; 259, 63, 22 and 39 for 2015; and 260, 52, 15 and 17 for 2016. The number of surgeries of the hypothalamic-pituitary area in children were 8, 9 and 7, in 2014, 2015 and 2016, respectively, whereas in adults were 35, 30 and 10. This means an overall decrease in the number of surgeries in the hypothalamic-pituitary area of 60.5% between 2014 and 2016, due, almost entirely, to the reduction of surgeries in adults (71.4%), and a global decrement of 50% in the number of adrenalectomies, while the number of thyroidectomies and parathyroidectomies remained stable during the study period, showing small interannual variation rates and annual averages of 261 and 57, respectively.
Conclusions
There is a strong and consisting trend towards a decrease in the number of surgeries in the hypothalamic-pituitary area (particularly in adults) and adrenalectomies during the last 3 years, while the number of thyroidectomies and parathyroidectomies has remained stable in the same period of time in our Tertiary-Care Referral Hospital. Further studies are required to evaluate the presence of similar trends in other medical centers of the rest of Spain and Europe, and, in case they are confirmed, analyze their causes as well as the potential associated economic impact in the medium and long-term.

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P647

New germline mutation of the *CDC73* gene in a Romanian family with hyperparathyroidism-jaw tumour syndrome

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Introduction
Hyperparathyroidism-jaw tumour (HPT-JT) syndrome is a rare autosomal dominant cause of familial hyperparathyroidism associated with ossifying fibromas (OF) of the maxillofacial bones and increased risk of parathyroid carcinoma, caused by inactivating germline mutation of the cell division cycle 73 (*CDC73*) gene.
Case report
We report the first Romanian family with HPT-JT and genetic screening of *CDC73* gene. Three of the six screened family members included in this study had biochemical evidence of HPT and surgically proven parathyroid tumours. The index case (female, 35 yrs; Ca = 13.9 mg/dl; PTH = 327 pg/ml) had a parathyroid carcinoma and had been previously operated for OF of the jaw and uterine fibroid. At the time of screening she was asymptomatic 5 yr after parathyroid surgery.There were no renal lesions and jaw tumors in other family members. Two of the three afected members had parathyroid carcinomas (the index case and one of her brothers, 44 yrs, persistent HPT after many surgeries Ca = 11.3 mg/dl; PTH = 193.7 pg/ml) and one had two parathyroid adenomas (the brother's son, 24 yrs, Ca = 12.2 mg/dl; PTH = 176 pg/ml). The genetic screening of *CDC73* gene (PCR amplification and direct Sanger sequencing on genomic DNA extracted from peripheral blood leukocytes) revealed that 4 of 6 patients showed a new heterozygous germline deletion of one nucleotide: c.128-IVS1 + 1 delG. The parents were alive and asymptomatic, the father been the carrier of the mutation; the index case' s daughter was negative for the mutation.
Conclusion
We identified a new germline mutation in a Romanian family of HPT-JT and confirmed the incomplete penetrance and the variable expression of the mutation.

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P648

Quality of life after medical versus surgical castration for locally advanced or metastatic prostate cancer

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Introduction
Metastatic or locally advanced prostate cancer is treated with surgical or medical hormone therapy. Preservation of the patient's quality of life is a major parameter that influences the management at this stage. Comparative studies between both types of hormone therapy that consider the patient's quality of life are almost nonexistent. The objective of our study is to evaluate the impact of medical and surgical castration on the quality of life in patients with locally advanced or metastatic prostate cancer.
Methods
A retrospective and comparative study including 200 patients with locally advanced or metastatic prostate cancer. 90 patients had medical castration and 110 patients underwent surgical castration. They were questioned about their quality of life using the â€oeexpanded prostate cancer index composits which includes urinary, digestive, sexual and hormonal evaluation.
Results
The two groups were comparable about age, clinical examination, tumor staging, histological results and initial rate of PSA. The difference between the two groups was statistically significant concerning digestive and hormonal evaluation. Indeed, strangury was more frequently found in patients having medical castration ($P = 0.03$). Intestinal transit disorders were also more frequently found in patients who had medical castration ($P = 0.03$). Hot flashes were more frequent and embarrassing in patients having medical castration than patients having surgical castration ($P = 0.1$ and 0.008 respectively). Nipple pain was more frequently found in patients with medical castration ($P = 0.02$). The two groups were similar about sexual and urinary evaluation.
Conclusions
Surgical castration is as effective as medical castration and has the advantage of better preservation of the patient's quality of life.

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P649

Endocrinological side effects of immunotherapy

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Introduction
The use of immunotherapy in oncology patients is increasing and is likely to continue to increase in the future. It is widely known that therapies have endocrinological side effects which can be serious, but maybe are also useful indicators to judge a response to the treatment. Presently, we do have not enough information regarding these side effects and their evolution.
Materials and methods
Observational and retrospective study of 162 oncology patients treated with immunotherapy in a third level hospital since 2014. Patients taking part in a double blind trial were excluded. The results were analysed with SPSS 24 package.
Results
Results from 162 patients were analysed (78% men, mean age of cancer diagnosis: 64 ± 11 years). 43% were treated with Nivolumab, 27% Pembrolizumab, 18% Atezolizumab, 3% Ipilimumab. 20 patients (12%) developed endocrine toxicity, with the thyroid being the most affected gland (11% of total patients). There was just 1 case of Hypophysitis, which occurred in a patient treated with Ipilimumab. 13% of patients treated with anti-PD1 had a thyroid disorder (60% hypothyroidism and 40% hyperthyroidism). Most side effects where reported with Nivolumab (55%), however, this was also the most frequently used drug and so it was deemed to be not statistically significant. The mean time between the first dose of the drug and the detection of the toxicity was 104 ± 129 days, separated by toxicities; hypothyroidism was developed in 80 ± 65 days (median 60 days) and hyperthyroidism in 142 ± 212 days (median 52 days). The evolution of these side effects in the thyroid gland, 88% of hypothyroidism and 29% of hyperthyroidism respectively, are persist. The case of hypophysitis persists.
Conclusions
Endocrine toxicity is a frequently observed side effect of immunotherapy with thyroid disorders being the most commonly reported, predominantly hypothyroidism. The incidence of our series is similar to other published series. The time to onset is variable, with a median of 2 months in the case of hypothyroidism. If hypothyroidism appears, it seems to be persistent but further long term studies are required.

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P650

Non-genomic effects of thyroid hormones on mesenchymal stem cells in tumour angiogenesis

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Tumour stroma formation is associated with angiogenesis and requires interactions of various different cell types, including endothelial cells and mesenchymal stem cells (MSCs), which are actively recruited into growing tumour stroma. Thyroid hormones T3 and T4 act as non-classical proangiogenic modulators mediated by non-genomic mechanisms via cell surface receptor integrin $\alpha v\beta 3$. The deaminated T4 derivative tetrac is a specific inhibitor of thyroid hormone action at the integrin site. The aim of this study was to evaluate the effects of T3 and T4 versus tetrac on MSCs in the context of angiogenesis. Treatment of primary human MSCs with T3 or T4 in the presence of hepatocellular carcinoma (HCC) cell-conditioned medium resulted in stimulation of expression of genes associated with angiogenesis as determined by qPCR. Additional treatment with tetrac reversed these effects. Primary human umbilical vein endothelial cells (HUVECs) were seeded on Matrigel and tube formation was analysed microscopically. Compared to untreated HUVECs, treatment with thyroid hormones and MSC-conditioned medium stimulated tube formation, while tetrac reduced tube formation. As the vascular endothelial growth factor (VEGF) is a critical angiogenesis mediator, we established a reporter gene system by placing the sodium iodide symporter (NIS) gene under control of the VEGF promoter. MSCs transfected with this construct (VEGF-NIS-MSCs) showed enhanced perchlorate-sensitive NIS-mediated iodide uptake activity *in vitro* after stimulation with HCC cell-conditioned medium and either T3 or T4 that was blocked by tetrac. T3 effects were additionally blocked both by the PI3K pathway inhibitor LY294002 and the ERK1/2 pathway inhibitor RAF265, while T4 effects were only blocked upon RAF265 treatment, supporting integrin $\alpha v\beta 3$-dependency. Effects of thyroid hormone on VEGF-driven NIS expression in MSCs *in vivo* were evaluated by iodide-124 PET in an orthotopic HCC xenograft mouse model. Tumoural radioiodide uptake demonstrated successful tumoural recruitment of VEGF-NIS-MSCs after systemic application followed by VEGF promoter-driven NIS expression. In hyperthyroid animals, a strongly enhanced radioiodide signal was detected in tumours compared to euthyroid and hypothyroid mice, while treatment with tetrac resulted in a markedly reduced signal. These data confirm the *in vitro* data suggesting significant thyroid hormone-mediated stimulation of VEGF in HCC tumours that was inhibited by tetrac. Our data suggest that thyroid hormones T3 and T4 influence angiogenic signalling in MSCs in an integrin-dependent fashion, providing further evidence of the critical role of thyroid hormones in the regulation of angiogenesis and the anti-angiogenic activity of tetrac in the context of tumour stroma formation.

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P651

Targeting Treatment Resistance in Breast Cancer Subtypes via LMTK3 Inhibition

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Introduction
LMTK3 is an oncogenic Receptor Tyrosine Kinase (RTK) implicated in resistance to endocrine therapy in breast cancer. Initially, LMTK3 was described as a regulator of Estrogen Receptor alpha ($ER\alpha$) since it was found able to protect it from ubiquitin-mediated proteasomal degradation. In a cohort of breast cancer (BC) patients ($n > 600$), LMTK3 protein levels and intronic polymorphisms were significantly associated with disease-free and overall survival and predicted response to endocrine therapy. These data were validated in an Asian cohort in which it was shown that LMTK3 was associated with more aggressive tumours. In addition, LMTK3 was demonstrated to contribute in BC invasion and migration. Recently, a new scaffolding function of LMTK3 was described that results in cancer progression through chromatin remodelling.
Aim
This study aims to identify selective LMTK3 inhibitors that can be used to enable pathway investigation and establish onward tractability of these compounds for future translational activities.
Materials and methods
The Bellbrook Laboratories Transcreener® assay kit was employed and 30,000 compounds were screened to detect novel LMTK3 inhibitors. Nearly 100 of them significantly inhibited LMTK3 activity and were therefore chosen for 10-point concentration-response profiling in duplicate and LC-MS analysis. The top 50 test compounds were clustered into unique chemotypes and were further tested using radiolabelled *in vitro* kinase assays. The top 5 compounds from two chemotypes were selected to be evaluated with hit-to-lead medicinal chemistry. Subsequently, an active site-directed competition binding assay (DiscoveRx KINOMEscan) was used to quantitatively measure the interactions between the top 5 hit compounds and more than 450 purified human kinases and disease relevant mutant variants.
Results and discussion
Two (C28 and C36) out of the 30,000 compounds that were screened inhibited by $>95\%$ the activity of only 10 and 8 kinases respectively. Moreover, the S(35) selectivity index of C28 was 0.186 while the selectivity index of C36 was 0.114. Interestingly, quantitative analysis of 38 kinase inhibitors currently used in clinical oncology showed a comparably low S(35) score as C28 and C36. It is expected that the crystallization of the LMTK3 kinase domain that is currently being conducted as well as co-crystallization experiments with these inhibitors and other analogues will guide a rational optimisation strategy of each chemotype.
Conclusion
More work is required; however, these data represent a step towards the development of the first LMTK3 inhibitors that may have potential for broad clinical utility in breast cancer.

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P652

Metformin and Simvastatin: a therapeutic combination to reduce the aggressiveness of glioblastoma multiforme

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Gliomas constitute the most frequent type of brain tumors and are characterized by a rapid growth and high diffusion through the brain. In particular, astrocytomas are a subtype of malignant gliomas that are graded from low to high aggressiveness (i.e. grade I, II, III and IV), being grade IV (glioblastoma multiforme, GBM) the most malignant type, and one of the most common cancers in the brain and CNS. To date, surgery is the first-line therapy combined with chemotherapy or radiotherapy; however, about two-thirds of patients do not have a survival rate greater than two years after diagnosis. Thus, it is necessary to develop new strategies to identify novel therapeutic targets for these devastating tumor pathologies. Metformin and Simvastatin are drugs commonly used to treat T2D patients and hypercholesterolemia, respectively. Interestingly, both compounds seem to exert anti-tumoral actions individually in different tumor types through AMPK-dependent and -independent pathways. Therefore, the aim of this study was to evaluate the anti-tumoral actions of metformin (10 mM) and simvastatin (10nM), individually and in combination, on key functional parameters (cell proliferation and migration rate) in human primary GBM cell cultures and GBM cell lines (U87 and U118), and to determine the signaling mechanisms behind these actions in GMB cells. We found that metformin and simvastatin alone inhibited cell proliferation in primary GBM cell cultures and GBM cell lines at 48 h and 72 h of incubation. Moreover, co-administration of metformin and simvastatin exerted an additive inhibitory effect on GBM cell proliferation compared to each compound alone. In addition, metformin, but not simvastatin, reduced cell migration in the U118 GBM cell line at 6 h, but not at 24 h, of incubation, whereas, co-administration of metformin and simvastatin significantly reduced the migration capacity of U118 GBM cell line at both incubation times (6 h and 24 h). Further analysis indicated that the anti-tumoral actions of metformin and simvastatin on GBM cells involve both common and distinct signaling pathways and are likely mediated through dissimilar molecular mechanisms. Altogether, our results demonstrate that metformin and simvastatin alone, and especially in combination, exert clear anti-tumoral effects in human primary GBM cell cultures and GBM cell lines, thus suggesting that these compounds deserve to be further explored as novel potential therapeutic tools for the treatment of patients with high-grade astrocytomas.

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P653

Inhibition of alternative splicing using the spliceosome inhibitor Pladienolide B reduces aggressiveness of prostate cancer cells *in vitro*

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Prostate cancer (PCa) is a complex and heterogeneous cancer that progresses from slow-growing, tissue-confined lesions, to highly aggressive and metastatic forms. Among the different processes involved in this progression, dysregulation of the alternative splicing mechanism, and, particularly, the generation of the spliced androgen receptor variant-7 (ARv7), plays a critical role in the pharmacological resistance of PCa patients (i.e. Abiraterone or Enzalutamide). In this context, recent studies have shown that Pladienolide-B, an inhibitor of the spliceosome (the molecular machinery that conducts alternative splicing), exhibits important anti-tumor effects in different cancer types; although, its role in PCa remains unknown. Hence, we aimed to determine the direct effects of Pladienolide-B in PCa cell-lines (LNCaP, 22Rv1, DU145, PC-3) and in normal prostate cells (RWPE-1 cell-line and primary cell-cultures obtained from cystoprostatectomies) by analysing different functional parameters such as cell proliferation, cell migration, tumorosphere formation and/or colony formation. Moreover, the expression of 45 splicing machinery components (major and minor spliceosome and splicing factors) was determined in the normal (RWPE-1) and tumoral (LNCaP/22Rv1/PC-3) prostate cell-lines in response to Pladienolide-B treatment by using a microfluidic-based qPCR array. Our results revealed that Pladienolide-B was able to reduce the proliferation of PCa cell lines, at 24-, 48- and 72-h in a dose-dependent manner (100 nM–0.01 nM), being this inhibitory effect significantly greater in PCa cell-lines compared to normal prostate cells (RWPE-1 and primary cell-cultures) at a dose of 100 nM. Interestingly, the antitumoral capacity of Pladienolide-B was corroborated by the inhibition of cell migration and tumorospheres/colonies formation in all PCa cell lines tested. Moreover, treatment with Pladienolide-B dramatically reduced the expression of proliferation markers (Ki67 and PTTG), EMT markers (Vimentin) and markers of PCa agressiveness (PCA3, androgen-receptor and ARv7 splicing variant) in PCa cell lines. Finally, Pladienolide-B was able to markedly alter the expression of numerous spliceosome components and splicing factors, some of them associated to higher PCa aggressiveness, such as SFPQ, KHDRSB1, SRRM4, NOVA1, ESRP1 and ESRP2. Taken together, our results demonstrate that Pladienolide-B clearly reduces PCa aggressiveness features *in vitro*, by the dysregulation of the expression of several splicing factors and tumor markers, suggesting a potential novel therapeutic role of this compound in PCa.

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P654

Fibroblast-kinome silencing to identifies putative mediator of Triple-negative breast cancer (TNBC) invasion

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Kinases represent a main therapeutic targets in cancer treatment as their impairing is related to tumor growth and progression. Despite the increasing evidence that tumor microenvironment (TME) signaling influences the behavior of surrounding cancer epithelial cells, still little is known about what changes in stromal cells influence tumor cells' behavior. TNBC patients are still lacking an effective therapy, as not much is known about the biology of this BC tumor subtype. TNBC trials focus mainly on targeting epithelial cancer cells by using a combination of kinase inhibitors and standard chemotherapy however these therapeutic regimens are not considering the action of stromal cells. **Our aim is to I**dentify fibroblasts-expressed kinases that modulate tumor cells' invasion and Characterize the mechanism by which these kinases promote/reduce tumor invasion.A library of SiRNA targeting 710 Kinases was used to transfect Human Mammary Fibroblast (HMF) and normal lung fibroblast (MRC5). 24h after transfection, fibroblasts were co-cultured with MDA-MB-231 for 3Dspheroids formation. Matrigel and chemoattractants were added to promote invasion that was evaluated by spheroids pictures analysis. kinases silenced spheroids were compared to controls. We identified PIK3Cδ, whose silencing decreased TNBC invasion rate, suggesting a pro-invasive role of this kinase. PIK3Cδ is essential for regulating chemokine production in leukocytes and promotes migration during inflammation. It has been shown that PIK3Cδ inhibitors (CAL -101) interfere in tumour-stroma interactions without directly killing cancer cells. Despite PIK3Cδ being expressed mainly in leucocytes, we detected high PIK3Cδ protein expression in various fibroblast cell lines and in primary fibroblasts derived from TNBC patients; however, PIK3Cδ was hardly detectable in a panel of breast cancer cell lines. Treatment with CAL -101, affected cell viability of fibroblasts cell lines, while it had limited/no effects on breast cancer cells. Fibroblasts treated with CAL -101 showed a decreased AKT phosphorylation, a downstream target of PIK3Cδ. Pretreatment of fibroblasts with CAL -101 significantly decreased TNBC cells' invasion in both 2D and 3D co-culture experiments. Interestingly, using transwell systems we found that co-culture with TNBC cells increased PIK3Cδ expression in fibroblasts, suggesting a feedback loop that 'fueled' tumor progression. Ongoing experiments are suggesting a paracrine signaling mechanism that may lead to the promotion of TNBC via PIK3Cδ fibroblasts expression. Using a novel 3D co-culture invasion assay, we identified stromal PIK3Cδ as a key mediator of TNBC invasion. Our results suggest that targeting PIK3Cδ in the tumor microenvironment may represent a novel strategy for TNBC therapy.

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P655

Expression of Toll/interleukin-1 receptor (TIR)-associated protein in primary hyperparathyroidism.

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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. Toll/interleukin-1 receptor (TIR)-associated protein (TIRAP) is an adaptor protein for Toll-like receptors-2 and -4 (TLR2/4) which are engaged in transducing the signal to downstream molecules. Several studies have shown the increased role of this protein in pathogenesis of hyperplastic lesions and neoplasm development.
Aim
The aim of the study was to assess the immunohistochemical expression of TIRAP 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 antibody anti-TIRAP. 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 6 counted high power fields (HPF, x 400). The sections were counterstained with Mayer's haematoxylin.
Results
The expression of TIRAP was significantly increased in parathyroid adenomas and hyperplasias compared to healthy parathyroid glands.
Conclusions
TIRAP might be useful in differential diagnosis between hyperplastic lesions of parathyroid gland.

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Expression of TICAM-2 in hyperplastic lesions of the parathyroid glands.

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Background
Even if a great number of studies have been developed recently, the molecular mechanisms of pathogenesis of hyperplastic lesions of the parathyroid glands are not well understood. The link between systemic inflammation and promotion of neoplasm is well established. Chronic infection and inflammation are considered two of the most prominent epigenetic and environmental factors contributing to tumor formation. Toll like receptors (TLRs) are essential components of innate immune system that protect the host against bacterial and viral infection. Toll/interleukin-1 receptor/resistance (TIR) adaptor protein (TICAM-2) can physically bind TIR domains and influence cell signaling. TICAM-2 interacts with TLR3 and mediates dsRNA activation of interferon-beta through NFkappaB.
Aim
The aim of the study was to assess the immunohistochemical expression of TICAM-2 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 antibody anti-TICAM-2. 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 6 counted high power fields (HPF, $\times$400). The sections were counterstained with Mayer's haematoxylin.
Results
Positive TICAM-2 immunoreaction was significantly increased in parathyroid adenomas, compared to hyperplasias and healthy parathyroid glands, whereas the expression of TICAM-2 was higher in hyperplasias than in controls. Positively stained cells were localized in the well vascularized region of the parathyroid nodule.
Conclusions
Our study indicated the important role of TICAM-2 in primary hyperparathyroidism and could be a potential therapetical targets. TICAM-2 might be useful in diagnosis of primary hyperparathyroidism. A better understanding of molecular profiling in primary hyperparathyroidism could result in more precise assessment of diagnosis and more effective treatment, especially in those cases in which the commonly used parameters are insufficient.

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Female Reproduction

P657

Dream recall and content vs the menstrual cycle: a cross-sectional study

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Introduction-Aim
Manifest dream content is rarely studied in dream research. Conflicting results have been presented regarding dream recall and affect vis-à-vis the menstrual cycle. Progestagens may improve dream recall. Thus, we aimed to assess dream recall/affect vis-à-vis the menstrual cycle in a large sample of women.
Subjects-methods
We studied 779 women (mean age $+$s.d.: $31+9$ years). The subjects were given once a simple questionnaire with items regarding age, menstrual cycle duration, day of their menstrual cycle, dream recall regarding previous night's dreams and dream affect/emotional content (positive or negative). We studied only women with self-reported regular menstrual cycles of 21–35 days in a cross-sectional fashion. We considered that the luteal phase of the menstrual cycle was relatively stable for all women, with a duration of 14 days. Statistical analysis was done with analysis of covariance, with dream recall and content as dependent variables, age as a covariate and menstrual phase as a factor.
Results
According to the subjects' responses 400 women were in the follicular phase and 379 in the luteal phase. Three hundred and two women recalled the previous nights' dreams, 159 reporting positive/pleasant dream affect/content and 143 reporting negative/unpleasant dream affect/content. Age was not associated with dream recall or content; the latter was not associated with menstrual phase ($P>0.5$). However, in women who recalled their dreams, there was a weak association of dream content with menstrual phase (and more in detail, of those with positive affect with the luteal phase, $P=0.06$).
Discussion
In women that recalled the previous nights' dreams a tendency towards pleasant dream content was noted in the luteal phase.

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Autoimmune thyroiditis and repeated pregnancy loss: a role for associated autoimmune disorders?

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Repeated pregnancy loss (RPL), defined as two or more spontaneous abortions, may be associated with autoimmune thyroiditis (AT), either isolated or associated with polyautoimmune disorders (PD), which include antiphospholipid syndrome. An increased occurrence of RPL has been reported in patients with isolated AT but very few data are available on the influence of concurrent auto-aggressive

disorders on RPL and this represented the aim of our study. A cohort of 1765 consecutively examined women with AT was retrospectively analyzed. Of these, 1501 had isolated AT and 264 had a simultaneous autoimmune disorder. Some 29% of women (516 out of 1765) had an abortion but only 87 (4.93%; median age = 28 years) had at least 2 abortions within the first 20 weeks of gestation. RPL rate was highly different when analyzed in women with isolated AT ($n=65$; 4.33%) and in those with PD ($n=22$, 8.33%; $P=0.0085$; OR = 2.01). Neither age nor thyroid function were significantly different in these subgroups at the time of first abortion. Similarly, no correlation between the levels of anti-thyroperoxidase antibodies and the number of abortion has been observed in both groups. Analyzing the role of thyroid function as source of bias, RPL rate appeared to be similar in hypothyroid women with isolated AT and with PD (1.8 vs 2.3%; $P=$ ns). On the contrary, among euthyroid women, RPL rate was higher in those with PD than in those with isolated AT (5.3 vs 1.9%; $P=0.0035$ OR = 2.842). In the subgroup of women, in whom successful pregnancy has never been observed ($n=15$; 17.2%), the occurrence of RPL was again lower in women with isolated AT than in those with PD ($P=0.0263$). In these latter, the presence of anti-phospholipid antibodies syndrome accounted for just 1/3 of RPL. These data indicated that the risk of repeated pregnancy loss in patients with thyroid autoimmunity is higher in the presence of further autoimmune disorders in an age- and function- independent way.

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P659

Audit of the management of adult patients with turner syndrome at the Nottingham University Hospitals (NUH), England

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Introduction
Turner Syndrome is a chromosomal disorder that is characterized by short stature and gonadal dysgenesis, affecting 1 in 2500 female live births. It is associated with a wide variety of conditions that could lead to significant morbidity and mortality if not followed up and managed appropriately. A multidisciplinary approach is important in the management of these patients. This audit aims to review the current practice of a specialist Turners Syndrome clinic in a secondary care hospital (Nottingham University Hospital, England) and to assess if standards of care are met.
Methods
A retrospective study of 37 patients who attended the clinic from Jan 2015 to Jan 2016 was done. Criteria based on two international guidelines were used. Information was gathered from local computer system which held tests reports and clinic letters.
Results
Median age of patients was 27 years old (range: 18–48). Areas well monitored (>85%) were bone health (with DEXA scan), U&E, LFT, VitD, calcium levels and the type of hormone therapy used. Areas less well monitored (50–85%) were thyroid function, coeliac screening, diabetes screening, ECHO and renal ultrasound. Areas that needed significant improvement (<50%) were audiology, lipid, FSH and LH level monitoring. 4 patients had an abnormal ECHO but only 1 went on to have an MRI. Only 24.3% of patients had a cardiac MRI. A majority of patients were on HRT (94.6%) but only 11.4% was on a transdermal form.
Conclusions
The audit showed varying performance in different areas. A standardized checklist and patient booklet for each patient review will be introduced to help identify tests due and to allow easy access to results that may have been done at another location. We would also consider doing more cardiac MRIs to pick up cardiac abnormalities that may have been missed on ECHO and to offer patients a switch from oral to transdermal HRT which is known to be more physiological.

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P660

Cognitive functions in adult women with turner syndrome

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Introduction
Turner syndrome (TS) is associated with specific physical features, as well as a particular neuropsychological profile and social and behavioral features. It is common practice in the case of TS to treat short stature with growth hormone preparations and to induce puberty with estrogens at an age as close to normal puberty as possible. Nevertheless results of some studies show that despite the treatment, some women with TS still experience psychosocial problems, impaired cognitive functions and lower quality of life. The aim of the study was to analyze cognitive functions in adult women with Turner syndrome.
Methods
A total of 65 women with genetically confirmed TS ≥ 18 yrs (age 30.2 ± 9.0 years) and 65 age-matched healthy women (age 29.2 ± 7.1 years, $P=0.807$) were recruited for the study. Cognitive functions were evaluated by Trail Making Test. Trail Making Test is a timed test in which the subject connects an altering sequence of numbers (Trail making A) or numbers and letters (Trail making B) in ascending order. The score on the Trail making A test, which is based on the time required to complete the sequence, is a measure of attention and visual scanning abilities. Trail making B is a test of executive function and psychomotor speed. A higher score denotes worse cognitive functioning. Sex hormones – Sex hormone-binding globulin (SHBG), Estradiol (E2), Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Dehydroepiandrosterone (DHEAS) and Testosterone (T) concentrations were measured in TS patients in the relationship with cognitive functions.
Results
Patients with TS were of a significantly shorter stature than age-matched control women (151.9 ± 6.8 cm vs 167.4 ± 5.9 cm, $P<0.001$). Trail Making A (42.7 ± 17.4 vs 26.2 ± 7.1, $P=<0.001$) and Trail Making B (86.0 ± 30.6 vs 53.8 ± 12.4, $P=<0.001$) showed worse cognitive functions in women with TS than in healthy age-matched women. Significant correlations between DHEAS ($r=-0.442$, $P=0.006$), T ($r=-0.465$, $P=0.003$) and Trail Making A test were found. The relation between T ($r=-0.426$, $P=0.006$), height ($r=-0,355$, $P=0,019$) and Trail Making B test in females with TS were identified, after adjusted for height the relation between T and Trail Making B remained insignificant ($r=-0.1503$, $P=0.136$). In conclusion, adult women with Turner syndrome have shorter stature and worse cognitive functions than age-matched healthy controls. The state of sex hormones and height in patients with Turner syndrome may be related with cognitive functions.

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Screening for liver abnormalities in turner syndrome: audit from a single centre

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Introduction
Liver involvement is frequent in Turner syndrome (TS) with a reported prevalence of abnormal liver function tests (LFTs) ranging 20–80%. Marked architectural changes and cirrhosis may be found in TS-women, associated with an increased incidence and risk of mortality.
Recent studies and guidelines recommended:
– monitoring annually all LFTs (International TS-Guidelines)
– to improve detection of liver disease, use Fibrosis-4 (FIB-4) score in patients with raised LTFs (EASL-EASD-EASO-Guidelines)
– perform abdominal ultrasound examination and liver stiffness measurement using Fibroscan in patients with unexplained elevated aminotransferases (EASL-EASD-EASO-Guidelines; Liver involvement in TS. *Roulot D.* Liver Int)
Aim
Audit to evaluate the current clinical practice in a large TS adult clinic in relation to the screening/management of liver abnormality against the aforementioned standards.
Methods
Data on 102 women with TS attending the adult TS-clinic over a one-year period (1/2015-1/2016) were retrospectively collected.
Results
Annually LFTs were performed in 98% of women for ALT, 37.2% for AST, 69.6% for GGT and ALP. There was a higher prevalence of LFT measurements among women who were previously diagnosed with LFT abnormalities, in particular for AST 33.9% (21/62) vs 42.5% in women with a history of LFT elevation and for GGT 66.1% (41/62) vs 75% (30/40).
Among patients with persistently elevated aminotransferases (20/102),
– FIB-4 was calculable in 55% (11/20) because of AST missing measurement, but only 54.5% (6/11) had a FIB-4 calculated

– 80% (16/20) were referred for liver ultrasound examination
– 50% (10/20) were referred for Fibroscan
Discussion
It is encouraging that LFTs were checked in the majority of TS-women, but AST being not part of the standard routine was only checked in 37%. There was a higher compliance for monitoring all LFTs among women who were previously known to have LFT abnormalities. The FIB-4 index was calculated in half of patients with persistently raised LFTs. The liver ultrasound was performed in the majority of women, while the Fibroscan was requested only in half of those. The newer investigations highlighted areas where the clinical approach with regard to the assessment/management of liver involvement in TS could be improved. We suggest the following strategies and a reaudit in one-year time: a) use pre-printed blood forms to include all LFT panel; b) add into the TS-clinic record form the previous LFTs results and related FIB-4 index; c) upload onto the clinic computers the online Fib-4 calculators; d) programme multidisciplinary meeting with the hepatologists.

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Cardiac evaluation in turner syndrome: echocardiography versus cardiac magnetic resonance

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Introduction
Women with turner syndrome (TS) have an increased risk of aortic dissection at young age. Bicuspid aortic valve (BAV) and aortic dilatation, both associated with TS, are risk factors. Preliminary studies suggested that cardiac MR (CMR) perfoms better than transthoracic echocardiography (TTE) for evaluating BAV and aortic dilatation, probably related to the frequent chest abnormalities in TS.
Aim
To evaluate the ability and comparability of TTE and CMR for detection of BAV and assessment of ascending aorta (AA) diameter in women with TS.
Methods
365 scans in 99 adult TS women: 287 TTE/94 women and 98 CMR/78 women (5 with no TTE). For TTE *versus* CMR AA diameter comparison, only scans performed within a 2-year period (78 scans) were considered. TTE and CMR exams were reviewed by TTE and CMR expert cardiologists.
Results
Assessment of BAV was difficult due to poor visualization with TTE in 31.9% (30/94) of patients and in 17.4% (50/287) of scans. In women with multiple TTE (74) 10.8% had discordant diagnosis. Valve assessement using CMR was not possible in 20.5% (16/78) of patients and in 17.3% (17/98) of scans. Among 73 patients with both TTE and CMR scans, CMR was concordant with TTE for the diagnosis of BAV in 56.2% (41/73), discordant in 9.6% (7/73), able to assess the valve in 13.7% (10/73) of women where were poorly visualized by TTE, and not able to assess the valve in 20.6% (15/73). The AA diameter was difficult to assess with TTE in 36.2% (34/94) of women and 16% (46/287) of scans. AA measurements were feasible in all CMR. Pearson's correlation between TTE and CMR AA measurements was $+0.723$ ($P<0.001$). Among scans performed with both techniques within a 2-year period, 72% showed a discrepancy between AA diameters:
- TTE underestimated CMR measurements in 32% (25/78) with a difference ≥ 3 mm in 16.7% (13/78).
- TTE overestimated CMR measurements in 40% (31/78) with a difference ≥ 3 mm in 18% (14/78).

In 10.3% of scans the results were the same and in 18% diameter was only measurable with CMR.
Conclusions
TTE assessment of BAV and aortic dilatation in women with TS is technically limited and frequently unreliable. CMR is the preferred imaging technique for overcoming the difficulties in assessment of aortic valve and aortopathy, and thus of aortic dissection risk, supporting the recent International TS Guidelines that recommend expert and multidiscliplinary approach.

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Growth hormone IGF axis - basic

P663

IGF-1 corellates with cognitive status in esrd patients undergoing haemodialysis

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Backrounds
Prevalence of cognitive function decline in End Stage Renal Disease (ESRD) patients undergoing hemodialysis is higher than in general population. We analyzed risk factors for cognitive function decline in those patients.
Study design
This study included 93 ESRD patients undergoing hemodialysis two or three times a week in Center for hemodialysis, Clinical center of Montenegro and two regional centers for hemodialysis in Montenegro. The cognitive status of patients was assessed using the Mini Mental Score Examination (MMSE) test. Laboratory data about risk factors for cognitive function decline was obtained in Center for clinical-laboratory diagnostic in Clinical center of Montenegro.
Results
All 93 patients have been divided into three groups according the results of MMSE. Patients in first group had severe cognitive impairment and MMSE score below 17 (26.88%), patients in second group with MMSE score 18–23 had moderate cognitive impairment (40.86%) and third group of patients have MMSE >24 and no cognitive impairment (32.26% of patients enrolled in study). There were no significant differences between groups for gender, smoking habits and level of parathyroid hormone. Level of schooling was significantly different between groups of patients ($P<0.001$). Laboratory markers observed in this study with significant differences between groups were: IGF 1, IGFBP 3, erythrocytes and hemoglobin ($P<0.001$, $P=0.004$, $P<0.001$, $P=0.002$ respectively). IGF 1 proved to be of great importance for evaluating cognitive status in our study. This marker was statistically different between groups ($P<0.001$) and Tukey post hoc analysis showed significant differences between all three groups (first and second group $P=0.045$, second and third group $P=0.015$, first and third group $P<0.001$).
Conclusion
Our data suggest that IGF 1 can be considered as novel biomarker for assessment of cognitive functioning in CKD patients what can be of huge clinical importance. This can be important and the particular new significance of this survey in relation to other studies.

Keywords: cognitive status, ESRD, hemodialysis, IGF-1
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IGF-I is not suppressed in adolescents submitted to resistance training and can be a marker of training status

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Background
Regular physical exercise during childhood and adolescence can promote growth and development of muscle and bone mass. Although physical exercise is closely linked to the anabolic function of the GH /IGF-I axis the real impact of resistance training on GH/IGF axis is still unclear. The kinetics of IGF-I and IGFBP-3 during chronic training is not fully understood yet and an initial catabolic phase followed by an later anabolic phase has been reported in swimmers.
Aim
The aim of the present study was to analyse the kinetics of IGF-I and IGFBP-3 in adolescents undergoing ten weeks of hypertrophy training.
Methods
Twenty-two male volunteers aged 18–25 years with at least 6 month experience in resistance training were enrolled and submitted to a standard hypertrophy training program during 10 weeks. Serum IGF-I and IGFBP-3 concentrations were determined before, 30 min-after and 24h-after the training session at the 1st, 5th and 10th week of resistance training. Body composition, lean mass, muscle mass, fat percentage and body mass index were also evaluated at the 1st, 5th and 10th week and compared to the changes in serum IGF-I and IGFBP-3. Data were paired compared.

Results
IGF-I levels increased during the training session at the 1st evaluation ($P=0.03$) and also increased during the 10 weeks of training ($P<0.003$). No changes in IGFBP-3 levels were observed during a training session or during the 10 weeks of training. Body mass, lean mass, fat percentage and body mass index of the volunteers remained unchanged throughout the 10 weeks of training. A negative correlation was observed between the changes in serum IGF-I concentrations and the variation in muscle mass or lean mass when data from the 1st and the 10th weeks were compared ($r=-0.62$; $P=0.002$).
Conclusion
In summary, no catabolic phase was detected in adolescents during hypertrophy training; IGF-I was sensitive to the acute and chronic effects of resistance training and can be considered as a biomarker of training status in non-athlete volunteers. The negative correlation between the variations in lean mass and IGF-I could suggest a training-induced increase in IGF-I sensitivity.

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Effects of zinc, magnesium and vitamin B6 (ZMA) supplementation on serum IGF-I, IGFBP-3 and Testosterone concentrations in young athletes

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Background
The GH-IGF system plays an important role in strength gain. Some studies suggest that Zinc, Magnesium and Pyridoxine (ZMA) supplementation could increase GH/IGF and testosterone levels in young subjects. This hypothetical increase could lead to significant changes in body composition. ZMA is a very popular supplement, easily found in specialty stores, and it is presumed to increase GH, IGF-I and testosterone levels. However, studies are divergent regarding its efficacy.
Aim
The present study aimed to verify the effects of physical training associated with 8-week ZMA supplementation on the IGF-I, IGFBP-3 and testosterone levels in young males.
Methods
Eighteen healthy male amateur American football players aged 18–25 years with at least 1 year experience in this sport modality were included in the study and followed during 8 weeks of training. The training consisted of a 90 min-conditioning session based on strength and aerobic exercises twice a week and specific tactic training also twice a week in different days. Energy intake and diet composition were determined by nutritionist. It was a double-blind study and the subjects were divided into two groups: ZMA and placebo groups according to the supplementation received. Anthropometric evaluation and blood sampling, for serum IGF-I, IGFBP-3 and testosterone determination, were performed at two different moments: at the beginning (M1) and after 8 weeks of supplementation (M2).
Results
Serum IGF-I and IGFBP-3 concentrations were higher at M2 in both groups. The increase was similar in the ZMA and in the placebo group. Testosterone concentrations were also higher at M2 than at M1 in a similar degree in both groups. The changes in anthropometric parameters that indicate lean mass gain or body fat mass reduction were similar in both groups.
Conclusion
The findings suggest that extra doses of the micronutrients present in the ZMA do not bring any additional benefits, either in the body composition or in the hormonal levels in subjects under adequate diet. Testosterone increase could partially explain the change in IGF-I and IGFBP-3.

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Neuroendocrinology

P666

Single center three years' experience with non-diabetic hypoglycemia in a tertiary hospital, Nepal

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Introduction
Diagnosis of hypoglycemia in non-diabetics is challenging in most of the cases. Appropriate diagnosis is possible only after taking proper history and performing appropriate laboratory investigation in appropriate time. The purpose of this study is to find the spectrum of etiology of hypoglycemia in non-diabetics in a tertiary hospital in a developing world with limited resources. This may help physicians working in similar situations.
Materials and methods
All patients admitted since June 2014 to June 2017 in the Tribhuvan University teaching hospital, Kathmandu for the evaluation of hypoglycemia were included in the study. Patients with diabetes and related hypoglycemia, gastric and intestinal/bowel surgeries, sepsis, starvation, cardiac, renal and hepatic failure in whom the cause of hypoglycemia was obvious were excluded from the study. In remaining twenty-one cases proper history was taken, and appropriate laboratory investigation was done. Two days of strict observation along with 72 h fasting and critical blood sampling for serum insulin and c- peptide was done.
Results
In twenty-one nondiabetic hypoglycemic patients, twelve were female and nine were male. The cause of hypoglycemia was presence of insulin autoantibody in five cases, adrenal insufficiency in five cases, reactive hypoglycemia in four cases, insulinoma in four cases, drug induced (excluding OHAs) in two cases and non-islet cell tumor hypoglycemia (Doege-Potter Syndrome) in one case. Six patients had autoimmune disease (Grave's disease in four cases, SLE in one case and RA in one case). Five cases were insulin auto antibody positive (except one patient with RA). Four out of five cases of adrenal insufficiency were due to secondary adrenal insufficiency. Among these four cases, three were female with Sheehan's syndrome. All four patients with reactive hypoglycemia were male and all of them presented to hospital for their concern about possibility of road traffic accident. Three out of four cases of insulinoma were male while one was female who also had associated primary hyperparathyroidism and later diagnosed as MEN 1 syndrome. In patients with drug induced hypoglycemia one was female diagnosed with RA who was taking hydroxychloroquine while another was a male taking ciprofloxacin for chronic pyelonephritis.
Conclusion
Insulin autoantibody related followed by adrenal insufficiency secondary to Sheehan's syndrome remains the commonest cause of hypoglycemia in non-diabetics in female while reactive hypoglycemia is the commonest cause in male.

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Does gender affirming hormone therapy affect anger proneness in transgender persons?

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Introduction
Anger is an emotional state of feelings varying from mild irritation to intense rage, whereas aggression implies externalizing angry emotions through destructive/punitive behavior towards other persons/objects. Although research on the relationship between testosterone and aggression is inconclusive, the WPATH SOC 7 guidelines have warned for an increase in aggression in transgender men (TM) taking testosterone treatment.

Aims
1. As aggression is initiated by angry feelings, we aim to assess whether anger proneness increases in TM and decreases in transgender women (TW) after initiation of gender affirming treatment.
2. To identify predictors for an increase (TM) or decrease (TW) of anger proneness.
Methods
This prospective cohort study is part of the European Network for the Investigation of Gender Incongruence (ENIGI). Anger was prospectively assessed in 440 TM and 468 TW by STAXI-2 (State-Trait Anger Expression Inventory 2) questionnaire during three year follow-up, starting at initiation of hormone treatment. Upon first clinical contact, participants filled in psychological questionnaires (Kreukels, 2012). Data were analyzed cross-sectionally and prospectively.
Results
Baseline STAXI-2 scores were comparable in TW and TM (15.0 (15.0–16.8) and 15.0 (15.0–16.0), $P=0.777$). TM showed a small increase in total STAXI-2 scores after three months, compared to baseline (+0.90, 95%CI 0.037–1.75, $P=0.041$), decreasing after one year (−1.296, 95% CI −2.15 to −0.44) to scores comparable to baseline ($P=0.235$), after which scores remained stable. At three months, there was no correlation between STAXI-2 scores and serum total testosterone or oestradiol levels, nor an association with co-existent psychiatric morbidities assessed by MINI plus and SCL-90R. At three months of testosterone treatment (cross-sectionally), TM reporting stronger negative affect (PANAS) experienced more anger proneness ($\rho=0.113$, $P=0.003$). Over 36 months in TM (prospectively), anger proneness was positively correlated to negative affect ($\rho=0.415$, $P<0.001$) and SCL-factors somatization ($\rho=0.075$, $P=0.033$), paranoid ideation/psychoticism ($\rho=0.101$, $P=0.004$), depression ($\rho=0.082$, $P=0.019$) and interpersonal sensitivity ($\rho=0.119$, $P=0.001$). In TW, STAXI-2 scores did not change over time ($P=0.952$). At three months, there was no correlation between STAXI-2 scores and serum testosterone.
Conclusions
Evidence from a prospective study shows no association between anger proneness and exogenous testosterone administration in TM. TM with psychological/psychiatric difficulties before gender affirming therapy are more likely to show a (temporarily) increase in anger proneness.

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Cigarette smoking and neuroreceptors genetic variations: a handshake between genetic and environmental factors leading to nicotine addiction

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Cigarette smoking is the major cause of disease related deaths in the world. Cigarette smoke contains many harmful chemicals, among them nicotine is the most potent one. The root cause of smoking hazards is nicotine addiction or dependence (ND). Environmental as well as genetic factors are reported to influence smoking which leads to nicotine addiction in all age groups especially. Neurexin1 is a cell adhesion protein important for synapse formation and *CHRNB4* is cholinergic receptor beta polypeptide. Studies have revealed a strong association between nicotine addiction and genetic variants in NRXN 1 and CHRNB4 genes in different world populations. Genetic associations of rs6721498 and rs17487223 SNPs of NRXN1 and CHRNB4 genes with ND were explored in Pakistani tobacco smokers. The questionnaire based data and blood and were collected from three hundred (300) individuals belonging to different ethnicities of Pakistan and categorized into non-smokers and smokers and habitual smokers. Based on Fagerstrom test, smokers and habitual smokers were categorized as Nicotine dependent and non-dependent. DNA was extracted and PCR-RFLP based genotyping of rs6721498 and rs17487223 SNPs performed for. Allele and genotyping frequencies were calculated and their associations with nicotine dependence was estimated. Association of nicotine dependence with anthropometric variables was also calculated. Allele Frequency of minor allele (A) of rs6721498 was 0.74 in nicotine dependent subjects and homozygous A/A genotype minor allele (A) increased risk of ND by 10.5 folds while allele frequency of minor allele (T) of rs17487223 was 0.56 and homozygous T/T genotype of minor allele (T) increased risk of ND by 8.44 folds. The socio-economic factors like education and tea/coffee intake increased risk of developing N.D by 5.76 and 3.32 times respectively while age, income status, ethnicity, Family history, stimulus, and obesity lacked significance of associations. Based on the highly strong associations of the minor alleles of both SNPs with nicotine addiction, it could be concluded that rs6721498 of NRXN1 and rs17487223 of CHRNB4 gene SNPs are risk markers of exploring nicotine dependence in Pakistani smokers. The environmental/socioeconomic parameters like caffeine intake and education also expressed significant association with ND. Subjects with Punjabi and Pothohari were more at risk of ND as compared to Pathan and other ethnic groups of Pakistan. Present study signifies role of genetic as well as environmental/socioeconomic risk factors that could lead to ND.

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Association of OPRD1 rs569356 SNP with Stress Response in opioid addicts

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As a lingering, often deteriorating brain disease, addiction causes neurotic drug seeking and utilization along with injurious significances to the addicts and to those living around them. Biological, genetic and a number of intrinsic and extrinsic environmental constituents are most vital in entire risk factors of drug addiction. Among addictive drugs opioid dependence is considered as the most deliberated drug abuse disorder and a major social dilemma worldwide. Opioids induce their action through opioid receptors. Among opioid receptors, the δ receptor encoded by OPRDI gene is involved in opioid addiction susceptibility. Genetic associations of polymorphisms in *OPRD1 gene e.g. rs569356 with heroin addiction are being reported in different world populations.* Opioid addiction has been strongly linked to stress conditions which increases craving for drug, development of addictive behaviors, as well as relapse to opioid use which in turn accelerates the major component of stress response system, Hypothalamus Pituitary Adrenal axis (HPA axis). Cortisol, as a final product of HPA axis of stress response in humans, is evaluated in blood serum of opioid addicts and thus could be used as a marker of stress response. The relationship between cortisol levels and *rs569356 SNP* in opioid addicts has not been explored yet. Keeping with the crucial roles of OPRDI receptor in drug addiction and cortisol as a stress response, present study was designed to investigate association of the risk allele of *rs569356 OPRDI variant with stress response in Pakistani opioid addicts. Whole blood samples from opioid addicts were collected for the extraction of g*enomic DNA and cortisol from serum. Genotyping of *rs569356 was carried out* by using allele specific PCR while cortisol levels were estimated by approaching ELISA. Allele frequencies were estimated through χ^2-test while association analyses were performed through regression models. Our results have shown high frequency of minor G allele of rs569356 (0.42) in drug addicts while the ancestral 'A' allele frequency was 0.58. Social and addictive behaviors including family history, guilt of addictive habits, family issues, and disturbance in daily routine significantly associated with drug addiction ($P=0.000$). The minor allele G of rs569356 SNP lacked association with opioid addiction but showed strong correlation with serum cortisol levels Our results confirm the role of minor G allele as risk marker of opioid addiction in Pakistani population through its role in elevating the stress responses (cortisol).

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Pro-inflammatory Socs3 inactivation in *Kiss1*-expressing cells does not affect reproduction and metabolism in mice

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It is well established that the kisspeptins are the main activators of GnRH neurons and therefore essential for the onset of puberty and reproduction. Previous studies have suggested that kisspeptin neurons are possibly major targets of pro-inflammatory cytokines to regulate reproduction. SOCS (suppressor of cytokine signaling) are proteins that regulate, as it says, cytokines. They inhibit the transduction of intracellular effects caused by those molecules, once that cytokines recruit multiple intracellular signaling pathways that can induce either acute or long lasting/genomic responses in several tissues. Among the different SOCS proteins, SOCS3 plays a major role regulating the sensitivity of pro-inflammatory cytokines. Considering that *Kiss1* mRNA coding is also found in other tissues besides the brain-related reproductive areas, the goal of the present study was to evaluate whether *Socs3* inactivation in kisspeptin cells may modulate the development and metabolism of mice. We bred the Kiss1-Cre strain with mice carrying loxP-flanked *Socs3* alleles. Mice carrying the kisspeptin-specific deletion were homozygous for the loxP-flanked *Socs3* allele and hemizygous for the Kiss1-Cre transgene (Kiss1 SOCS3 KO), whereas their control group was composed of animals containing a homozygous loxP-flanked *Socs3* allele. Sexual maturation was evaluated daily by determining the age of balano-preputial separation and by the age at vaginal opening, the first occurrence of vaginal cornification in the vaginal lavage (first estrus) and the first occurrence of an estrus cycle of normal duration. Body weight was recorded weekly and at every event of sexual maturation observed. Adult mice were submitted to glucose and insulin tolerance test or to a lipopolysaccharide S (LPS) acute injection. The adult animals were euthanized and adipose fat pad was collected. We observed that the sexual maturation of mice was not affected by specific *Socs3* inactivation. No significant differences in body weight during development or adipose fat pads weight at adult age were observed between groups. Glucose and insulin sensitivity were similar between Kiss1 SOCS3 KO and control mice. Additionally, by using a model of acute inflammation we observed that specific *Socs3* inactivation did not modulate the anorectic effects of inflammation induced by LPS. Our results demonstrated that *Socs3* inactivation in *Kiss1*-expressing cells, does not affect the development of mice. Suggesting that the previous observed role of the kisspeptin neurons as targets of pro-inflammatory cytokines may be indirect or depend on other signaling pathway not assed in the present work.

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Abstract withdrawn.

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Abstract withdrawn.

Nuclear Receptors and Signal Transduction

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Vitamin D abolishes the dexamethasone-induced apoptosis in acute myeloid leukemia cells via regulation of Notch signaling

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Introduction
Glucocorticoids are used for treatment of various hematological malignancies such as Acute Myeloid Leukemia (AML). Glucocorticoids are known to induce apoptosis by regulating the expression of key anti- or pro-apoptotic genes. Vitamin D induces apoptosis and cell cycle arrest in various types of cancer cells. Despite recent advances in treatment of AML, the poor response rate to therapy remains a big challenge.Therefore, discovering new factors that can affect therapeutic response to Glucocorticoid therapy is mandatory.
Aim
I) to investigate the effect of $1,25(OH)_2$vitamin D_3 (VitD) on glucocorticoid-induced AML cells apoptosis and/or cell cycle arrest, II)to determine whether this effect is mediated through activation of Notch-1 signaling.
Methods
Kasumi-1 cells were either incubated for 72 hours with dexamethasone (Dex-10^{-6}M and 10^{-7}M) alone or pre-incubated with VitD (10^{-7}-10^{-9}M) for 24 h. MTS assay was performed to quantify viable cells whereas apoptosis was measured by flow cytometry (Annexin V/PI staining). The mRNA expression of *Mcl-1, Noxa, Bcl-2, Bax, p21, Notch-1 and Notch-2* genes implicated in apoptosis and cell cycle arrest, was evaluated by qPCR. Notch-1 and cleaved Notch-1 (NICD-active-form) protein levels were measured by Western blot.
Results
The results of MTS and FACS indicate that Dex induced apoptosis in Kasumi cells dose-dependently, however this effect was attenuated significantly in cells pre-incubated with VitD. Pre-incubation of cells with VitD for 24h followed by co-incubation with Dex for further 72h increased the Bcl-2/Bax ratio significantly via reducing the Bax mRNA expression while did not change the mRNA MCL-1/NOXA ratio compared to those cells incubated with Dex alone. P21 mRNA expression was reduced significantly in cells pre-incubated with VitD compared to cells incubated with Dex alone. The Notch-1 and its intracellular domain protein levels was not detectable in the presence of dexamethasone at lower concentration. The protein level of Notch-1 as well as NICD were significantly increased in cells pre-incubated with VitD (10^{-8}M) and then co-incubated with Dex (10^{-7}M) as compared to cells incubated with Dex (10^{-7}M) alone.
Conclusions
VitD exerts inhibitory effect against Dex induced-apoptosis in Kasumi-1 cells via increasing Bcl2/Bax ratio, while MCL-1/NOXA ratio did not seem to play important role. VitD can induce cell survival by inhibition of GC-mediated cell cycle arrest through activation of Notch-1 signaling, which could in turn result in reduction of p21 expression.

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1,25 dihydroxyvitamin D reverses everolimus resistance in hepatocellular carcinoma activating mesenchymal-epithelial transition and miR-375

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HCC is a difficult-to-treat-cancer with poor prognosis. EVOLVE-1 trial demonstrated that EVE did not improve overall survival in molecularly and clinically unselected patients with advanced HCC resistant to sorafenib. In selected patients, the well-established antitumor effect of EVE could make this a potential adjuvant therapy. Unfortunately, EVE acquired resistance due to the

tumor adaptation to chronic drug use is a current challenge. VitD was deemed as potential regimen to treat several cancers alone or in combination with other drugs. The aim of this study was to explore the role of VitD pre-treatment in the re-sensitization to EVE in two models of HCC cell lines, PLC/PRF/5 and JHH-6 cell lines resistant to EVE (PLC/PRF/5 EveR and JHH-6 EveR). EveR cells were obtained after 4 months of treatment with EVE 10^{-8}M. VitD receptor (VDR) expression was confirmed by RT-qPCR and WB. DNA assay was established to evaluate the proliferation rate in parental and EveR cells after EVE treatment (from 10^{-14}M to 10^{-8}M) alone or in combination with VitD (10^{-7}M). Epithelial–mesenchymal transition (EMT) markers were evaluated by IF in parental and EveR cells, even after VitD treatment. miRNA PCR Arrays were employed to investigate the difference in parental and EveR cells after 12hrs of treatment with VitD. EVE long-term exposure increased mRNA and protein VDR expression in PLC/PRF/5 EveR but not in JHH-6 EveR cells. Contrary to EveR, in parental cells, EVE significantly reduced cell proliferation in a dose-dependent manner after 6 days of treatment where VitD did not improve EVE effect. In both EveR cells 12 and 24hrs of VitD pre-treatment was sufficient to significantly restore EVE efficacy at concentration ranging from 10^{-14}M to 10^{-8}M. In EveR cells, EVE 10^{-8}M chronic treatment increased the protein expression of mesenchymal markers, but VitD prolonged treatment restored epithelial markers protein expression. miRNA expression analysis in EveR cells revealed miR-375 downregulation compared to parental ones, conversely, EveR cells treated with VitD for 12hrs showed miR-375 upregulation compared to EveR cells. Treatment with VitD was able to downregulate metadherin and Yes Associated Protein 1, genes involved in drug resistance and bioinformatically predicted miR-375 target genes, expression in both EveR cells. These data suggested the use of VitD to overcome EVE acquired resistance in HCC reverting EMT and downregulating the expression of genes involved in drug resistance acting trough the regulation of miR-375.

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Inactive AT1 angiotensin receptor acts as a signaling hub: a novel mechanism of receptor cross-talk

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It is generally believed that the signal transduction of AT1 angiotensin receptor (AT1R), the major receptor of angiotensin II, requires ligand binding and subsequent adoption of its active conformation. Activated AT1R induces a plethora of signaling pathways, in contrast to inactive AT1R, which was thought to be silent in terms of signaling. We hypothesized that unliganded, but phosphorylated AT1R may recruit β-arrestins, the key proteins of receptor desensitization, internalization, and signaling. Since phosphorylation of AT1R is induced by a variety of other receptors, the β-arrestin activation by heterologously-phosphorylated AT1R may represent a novel mechanism of signal transduction and receptor cross-talk.In this study, we demonstrated that activation of protein kinase C (PKC) by phorbol myristate acetate, Gq/11-coupled GPCR or epidermal growth factor receptor stimulation promotes β-arrestin2 recruitment to AT1R even in the absence of AngII. We also provided evidence that endogenous purinergic receptors can exert the same effect, proving that the interaction can be triggered at physiological levels of PKC activation. We found that heterologous mechanisms of β-arrestin recruitment to AT1R does not demand the active state of the receptor and was dependent on the stability lock. This interaction required the association of phosphorylated serine-threonine clusters in the receptor's C-terminus and two conserved phosphate-binding lysines in the β-arrestin2 N-domain, resulting in sustained binding between these proteins. Using improved FlAsH-based β-arrestin2 conformational biosensors in BRET (bioluminescence energy transfer) measurements, we showed that β-arrestin2 binds to PKC-phosphorylated AT1R in a distinct active conformation, which triggers MAPK recruitment and receptor internalization. Our results reveal that AT1R may also function as a scaffold protein, demonstrating its novel role in signaling and receptor cross-talk.This work was supported by the Hungarian National Research, Development and Innovation Fund (NKFI K116954 and NVKP_16-1-2016-0039).

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Obesity

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Gender specific differences in patients with metabolic syndrome and major depression

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Background
Metabolic syndrome (MetSy) comprises a cluster of risk factors (central obesity, high blood pressure, low high density lipoprotein [HDL]-cholesterol, elevated triglycerides and hyperglycaemia) associated to the risk of cardiovascular diseases development. Depression has also been reported to be associated with an increased risk for diabetes and cardiovascular diseases, the underlying mechanisms being still poorly described. MetSy may mediate this association, but only limited data have been reported to support whether MetSy and depression are connected, and, moreover, whether this connection is gender-specific.
Objectives
The study aimed to evaluate the gender differences in patients with MetSy and depression.
Methods
Seventy patients with major depressive disorder (MDD) and MetSy were studied. The MDD was diagnosed according to DSM-IV-TR. MetSy was screened for considering the International Diabetes Federation consensus worldwide de-finition of the Metabolic Syndrome.
Results
The study group comprised 45 women and 25 men hospitalized for MDD (gender ratio F:M = 1.8), with an average age of 45.34 ± 5.43 years. The mean age of onset of the MDD was 41.12 years. The group of patients associating MDD and MetSy consisted of 15 women and 11 men (gender ratio 1.36, with no significant statistical difference). The female subjects associating MetSy met 4 or even 5 diagnosis criteria, compared to the male subjects, who generally met only 3 diagnosis criteria. The most frequent MetSy diagnosis criteria were high blood pressure, increased levels of triglycerides and increased levels of glucose, with no statistical significant differences between the male and the female groups. The maximum range of systolic blood pressure was higher in the female group compared to the male group (195 mmHg *vs.* 165 mmHg, P = 0.03). There was a significant difference in the mean triglyceride level: the female group had higher values compared to the male group (mean value 229.7 mg/dL *vs.* 212.31 mg/dL, $P < 0.05$). The female group had also higher HDL-cholesterol levels (mean value 44 mg/dL *vs.* 35 mmol/L, $P = 0.04$).
Conclusions
The metabolic syndrome is associated with depression irrespective of gender. Patients with depression may be prone to metabolic syndrome both because of poor health-related behaviours and lifestyle, and antidepressant medication, causing prolongation of the depression episodes, increasing the percentage of relapses, and lowering the adherence to treatment. These findings highlight the importance of screening for depression in patients with metabolic syndrome, as lifestyle changes could reduce the visceral adiposity and inflammation that might ameliorate depression.

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Paediatric Endocrinology

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Awareness & participation in rare disease registries within the European reference network on rare endocrine conditions (Endo-ERN)

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Background
Registries are of key importance for a centre of expertise. Endo-ERN consists of 71 reference centres (RCs) that cover several groups of rare endocrine conditions within 8 themes (www.endo-ern.eu). It is unclear if awareness, participation and availability of registries is uniform for all conditions within Endo-ERN.
Objective
To determine the extent of engagement in registries of Endo-ERN members.
Methods
Endo-ERN RC leads were invited to participate in a survey of their awareness and participation in local, national and international registries and their views on future priorities using a Likert scale of 1–5 where 5 was the greatest priority.
Results
A RC response rate of 82% was obtained. Of the 29 centres surveyed within the glucose theme, 62% reported an awareness of an international registry for rare diabetes with a 48% participation rate. A priority score of 5 was only attributed to rare diabetes. Of the 33 centres within the adrenal theme, awareness of an international registry was 61% for adrenocortical tumours (ACT) and participation was 39%. Pheochromocytoma, ACT and CAH were rated as 5. Of the 37 centres within the sex development theme, 50% reported awareness and participation was 37% for DSD; all conditions were rated as 5. Of the 43 centres within the pituitary theme, international registry awareness was 33% for pituitary adenoma whilst participation was 23%. Pituitary adenoma was the only condition rated as 5. Of the 31 centres within the rare genetic tumour theme, 19% reported an international registry awareness for MEN1 and 6% reported participation; all conditions were rated as 5. Of the 30 centres within the growth theme, international registry awareness was 17% for Prader Willi Syndrome and participation was 10%. All conditions were rated as 5. Of the 29 centres within the Calcium/Phosphate theme, international registry awareness was 14% for phosphate disorders and participation was 7%. Hypocalcaemia and hypophosphataemia were rated as 5. Of the 35 centres within the thyroid theme, international registry awareness for thyroid carcinoma was 14% and participation was 0%, with 4 of 6 conditions being rated as 5.
Conclusion
Whilst there is a clear need to develop new detailed disease registries, there is also a need to improve the awareness and signposting of existing registries. A common platform that is used by the whole endocrine community and which directs the user to high quality detailed disease registries has the potential to achieve this objective.

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Long-term endocrine sequelae of patients with beta-thalassemia following bone marrow transplantation in childhood/adolescence

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Introduction
Allogeneic bone marrow transplantation (BMT) represents the only effective approach to the cure of thalassemia major, offering high rates of success especially in a pediatric setting. Endocrine complications are expected in these patients due to both primary disease and BMT process. Iron overload, desferrioxamine treatment, cytotoxic agents used in the preparative regimen, and posttransplant immunosuppression period contribute to various endocrine disorders.
Aim
To evaluate the long-term endocrine sequelae of patients with thalassemia major (TM) who underwent bone marrow transplantation (BMT) during their childhood/adolescence.
Patients and Methods
The records of patients with beta thalassemia who received bone marrow transplant during their childhood/adolescence and were followed in an Adult Endocrinology Unit were reviewed.
Results
A total of 11 patients (5 males and 6 females) who were transplanted from an HLA matched donor were identified. Their median age at bone marrow transplantation was 13(3–17) yrs. At last assessment, their median age was 28 (19–33) years old, their median height 165 (158–170) cm, their weight 65 (50–85) kg and their BMI 24.1 (17.5–29.4) kg/cm^2. Median follow-up duration was 15 (6–21) years.At last assessment 5/11 (45.5%) had hypothyroidism, and were on thyroxine replacement, 8/11 (72%) had osteopenia/osteoporosis, 2/11 (18.18%) had hypogonadotrophic hypogonadism and 9/11 (81.81%) had hypergonadotropic hypogonadism. All females and 3 males were on gonadal steroids. Two women had conceived spontaneously while on hormone replacement therapy and their pregnancies were both uneventful. None of the patients had adrenal insufficiency and diabetes mellitus. Two females had developed genitalia graft versus host disease (GvHD).
Conclusions
Although allogeneic BMT is known as the only definitive treatment of thalassemia major, it cannot eliminate all potential risks of endocrine dysfunction. Our results indicate that clinical findings of organ dysfunction may present or remain in the late period. Therefore, patients should be monitored for endocrine and other late complications as chronic graft-versus-host disease (GVHD) after BMT regularly.

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Non-classical congenital adrenal hyperplasia: the most frequent mutations

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Background and Objective
Congenital adrenal hyperplasia (CAH) is one of the most common diseases in pediatric endocrinology. Non-classical (NC-CAH) forms are characterized by milder enzyme dysfunction and manifests commonly in adolescence or adulthood. The most frequent form of NC-CAH occurs due to 21-hydroxylase deficiency which is caused by defects in the CYP21A2 gene. Our aim was to describe the most common 21-hydroxylase gene (CYP21A2) mutations in our geographical area in pediatric patients with clinical and biochemical diagnosis of NC-CAH and to determine bone age advance respect to Chronological age at diagnosis moment.
Setting and Method
A genetic study of the most frequent 21-hydroxylase mutations was requested in prepubertal patients with clinical and biochemical diagnosis of NC-CAH. Bone age at diagnosis was also determined using the Grewlich and Pyle reading methods. Main outcome measures 21-hydroxylase gene (CYP21A2) mutations.
Results
We evaluated 18 patients (12 women and 6 men) with a mean age at diagnosis (mean $\pm$ SD) of 7.61 $\pm$ 2.23 years. The most frequent clinical presentation was precocious puberty (66.7%) followed by virilization (22.2%) and precocious puberty + apocrine sweating (5.6%); in 1 patient the genetic study was requested for a family history of NC-CAH without symptoms. In the genetic study, the most frequent genotypes were: V281L in heterozygosis (61.1%) and homozygosis (11.1%), I2splice in heterozygosis (5.6%), V281L/I2splice (5.6%), V281L/P453S (5.6%), P453S in heterozygosis (5.6%) and Cluster E6/V281L/L307 frameshift/Q318X (5.6%). Of the 36 alleles studied, the V281L mutation was found in 75%. Mean bone age advance was 1.83 $\pm$ 0.71 years.

Conclusion
The NC-CAH is more frequent in the female sex, precocious puberty is the most common symptom and the V281L mutation is the most frequent in our environment. The patients affected usually present bone age advance respect to the chronological age at diagnosis.

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Steroid Metabolism + Action

P680

Characterization of sex hormone binding globulin ligands with potential to enhance sex steroid action

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Sex Hormone binding globulin (SHBG) is a plasma steroid binding protein that is the major determinant androgen and estrogen access to target tissues. Several ligands of SHBG have been predicted by computational methods or discovered through basic research, they include pharmaceutical, natural plant extracts and anthropogenic endocrine disrupting compounds. In this study we characterized 3,4-Divanillyltetrahydrofuran (DVT), a non-steroidal ligand of SHBG, and Danazol, a synthetic steroid-like molecule, using X-ray crystallography, steroid binding capacity assays, and cell reporter assays. DVT is present in organic extracts of Urtica dioica root that are used in natural health supplements to enhance the anabolic activities of testosterone by virtue of its ability to displace testosterone from SHBG. Danazol treatment has been used pharmaceutically to treat endometriosis, but more recently has been reported to lead to telomere elongation; an effect that is known to estrogen-dependent and may be related to the ability of Danazol to displace estradiol from the SHBG binding site. The binding affinities of DVT and Danazol for SHBG, are 1.47% and 2.81%, respectively, relative to that for testosterone. The crystal structure of E176K SHBG LG4 Domain with DVT or Danazol in the binding site was solved to 1.7 Å and 1.75 Å resolution, respectively. Danazol resides in the SHBG steroid-binding site in essentially the same orientation as Dihydrotestosterone (DHT) and like DHT its binding affinity was unaffected by Zn^{2+}. By contrast, the binding pose of DVT in the SHBG steroid-binding site was similar to those of estrogens, resulting in a similar positioning of key residues in and around the binding pocket, and as observed from estrogens the SHBG binding affinity for DVT is substantially reduced in the presence of Zn^{2+}. These results indicate that the SHBG binding site can accommodate ligands with structures that diverge significantly from the natural steroid structure. To examine the physiological relevance of DVT binding to SHBG, we used an *in vitro* luciferase reporter assays of androgen receptor activity in kidney cell lines. This showed that DVT is capable of displacing DHT from SHBG in media, resulting in dose dependant increase in androgen receptor mediated luciferase reporter activity, thus confirming that non-steroidal ligands of SHBG can displace natural steroid from their SHBG binding site and may be of utility in promoting the biological activities of endogenous sex steroids.

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Relationship between salivary cortisol circadian rhythm and body composition in the postmenopausal women of the population cohort OsteoLaus

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Introduction
Aging is associated with a decrease in muscle and bone mass, and a gain in fat mass. Similar changes are more pronounced in hypercortisolism. We previously demonstrated that high 8 PM salivary cortisol is independently associated with increased prevalence of radiologic vertebral fractures. We wanted to determine whether salivary cortisol circadian rhythm played also a role on body composition.
Material and Methods
Cross-sectional study including 538 women >50 years old (mean age 63.6 ± 7.5) from the OsteoLaus cohort. Included participants had: body composition assessment by DXA, salivary cortisol circadian rhythm measures (awakening, 30 minutes thereafter, 11 AM and 8 PM) and assessment of handgrip. On top of body composition parameters, sarcopenia prevalence, as defined by the EWGSOP group (appendicular lean mass by height squared (ALMI) $<$ 5.5 kg/m^2 and muscle strength $<$ 20 kg), was analyzed.
Results
Salivary cortisol at 11 AM and 8 PM increased with age. We found no association between salivary cortisol circadian rhythm values and fat distribution (total fat, fat mass index, or visceral fat). Neither total lean mass, nor ALMI were separately associated with salivary cortisol measures. There were 15 sarcopenic participants that were older (67.5 ± 7.5 vs. 63.4 ± 7.5 yo) and had lower BMI (20.4 ± 2.8 vs. 26.2 ± 4.6 kg/m^2). Sarcopenia presence was positively associated to 11 AM and 8 PM values in monovariate analysis and after adjustment to age and BMI (adjusted p-values 0.021 and 0.044, respectively). Sarcopenic participants had significantly higher values of salivary cortisol than not sarcopenic participants at 11 AM (13.1 ± 6.5 vs. 9.2 ± 4.5 mmol/l) and 8 PM (5.1 ± 5.1 vs. 3.3 ± 2.1 mmol).
Conclusions
Salivary cortisol values are not associated to fat neither lean mass distribution as assessed by DXA. However, highest values at nadir time points 11 AM and 8 PM are associated to sarcopenia prevalence as defined by the EWGSOP group, independently of age and BMI. If these results are confirmed in other studies, the measurement of salivary cortisol at 8 PM may play a role in the assessment of sarcopenia.

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Proteolytically cleaved forms of corticosteroid-binding globulin with low steroid-binding affinity are not present in human plasma

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Corticosteroid-binding globulin (CBG) transports glucocorticoids in blood and is a serine protease inhibitor family member. Plasma CBG has a reactive center loop (RCL) structure that when cleaved by specific proteases, including neutrophil elastase, results in a loss of high affinity steroid-binding activity. Measurements of CBG levels are typically based on functional assays of its steroid-binding capacity or immunoassays, including enzyme-linked immunosorbant assays (ELISAs). Recently, CBG levels have been measured using different ELISAs that rely on monoclonal antibodies that discriminate between CBG molecules with an intact versus a cleaved RCL. In blood samples from healthy and diseased individuals, discrepancies in CBG levels measured using these ELISAs have been interpreted as evidence for CBG with a cleaved RCL and a low affinity for cortisol. We have questioned these assumptions by studying the steroid-binding activity and biochemical properties of CBG in blood samples in which there is a clear discrepancy in ELISA measurements. In addition, we sought to identify RCL-cleaved forms of human CBG in blood samples from patients suffering from acute inflammation in an intensive care unit (ICU) setting, in whom plasma CBG levels are very low. Our results found no evidence for cleavage of the RCL in CBG in blood samples from ICU patients, irrespective of whether their CBG ELISA measurements were concordant or discrepant. The absence of CBG with a cleaved RCL was also demonstrated using a heat-ramp polymerization assay in a serum sample that exhibits a discordancy in ELISA values. Moreover, when a monoclonal antibody designed to specifically recognize an intact RCL was used to immuno-absorb CBG from a discrepant sample, the residual CBG molecules had the same high affinity (Kd $\sim$1.75 nM) for corticosterone as CBG in the sample prior to immuno-absorption (Kd $\sim$1.72 nM) or in samples in which there is no discrepancy in ELISA values. It is therefore suggested that in some

samples, CBG molecules react abnormally to ELISAs because of structural differences that influence the epitopes recognized by specific monoclonal antibodies.

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Thyroid (non-cancer)

P683

Role of Pro-inflammatory biomarkers in Hashimoto's thyroiditis: A prospective study

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Introduction
Hashimoto's thyroiditis (HT) is one of the commonest organ specific autoimmune thyroid disease. Though it is mostly treated medically, certain goitrous forms require surgical thyroidectomy for various indications. Autoimmunity has been implicated as one of the main cause of HT. In this context, we set out study the role of Pro- inflammatory cytokines in HT.
Material and methods
This prospective case-control study was conducted on surgically managed HT patients. Institutional ethical committee approval was obtained. Diagnosis of HT was based on thyroid function tests, anti-TPO antibody titer, radionuclide scanning and histopathology. Exclusion criteria were subjects any systemic or chronic inflammatory disease or any medication which interferes with the normal function of the hypothalamic-pituitary-gonadal axis. Serum samples were collected from 25 HT subjects and 25 age matched healthy controls. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF-α) and high sensitive C reactive protein (hsCRP), Leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.
Results
The mean hSCRP level in GD and controls were 14.7 ± 2.9 mg/mL and 6.5 ± 1.7 mg/mL respectively. The mean TNF-α level, IL-6 level and Leptin levels were 234 ± 26 pg/mL, 12.6 ± 4.5 pg/mL and 32 ± 4.9 ng/mL respectively. There was statistically significant difference of all the pro-inflammatory cytokines compared to controls (P value < 0.05).
Conclusions
This study shows raised titers of pro-inflammatory markers – IL-6, TNF-α and hsCRP, leptin correlated with HT suggesting a contributory role. But, the exact immuno-modulatory role and pathogenetic mechanism needs active research.
Keywords: Hashimoto's thyroiditis, Tumour necrosis factor, Interleukin-6, Goiter, Auto-immunity, Leptin

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Autoimmune thyroiditis and chronic spontaneous urticaria – case series

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Introduction
Chronic spontaneous urticaria (CSU) has many links to autoimmune disorders, one of a described association being with autoimmune thyroiditis. The prevalence of thyroid antibodies is as high as 50% in patients with CSU. However, the pathogenic mechanism whereby thyroid autoimmunity is link to CSU is still poorly understood.
Methods
We have analysed a case series of 20 patients with chronic urticaria and elevated TPO-antibodies, that have been presented in our departments of endocrinology and allergology within one year. After excluded all other causes of hives, patients had blood sample for thyroid antibodies and hormone levels, the eosinophil blood count, inflammatory markers, serum protein electrophoresis and immunoglobulin levels.
Results
We had 20 female patients. 11 of them (55%) were euthyroid; 4 had hypothyroidism (20%) – 3 subclinical and one overt hypothyroidism; 5 patients had hyperthyroidism (25%) – 3 subclinical and 2 patients with clinical hyperthyroidism (one with Basedow 's Disease and one with Hashitoxicosis). We observed a biological particularity: 2 patients had associated histamine intolerance, with low level of diamine oxidase (DAO) activity, in both cases normal thyroid function.
Conclusion/Comments
The association of chronic spontaneous urticaria and autoimmune thyroiditis can hide a genetic predisposition to autoimmune diseases. It is possible that they have a common pathogenic pathway. In large studies hypothyroidism is more common than hyperthyroidism; we had more hyperthyroid patients, but just one developed Basedow's Disease, all of the rest having a mild hyperthyroidism as an early phase of chronic autoimmune thyroiditis. There have been only a few reports on the pathophysiology of reduced DAO activity in CSU. It is known that a low activity is linked with bowel inflammation and there is an individual variability in DAO expression in epithelial cells. There has been so far no causal link between autoimmune thyroiditis and reduced DAO activity. Our 2 patients had normal thyroid function and, maybe, the links could be genetic. More studies are needed to elucidate the role of thyroid function and TPO-Abs in chronic urticaria.

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Thyroid cancer

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Late diagnosis of type 2B multiple endocrine neoplasia (MEN 2B) in a 24-year-old patient

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We present the case of a 24-year-old melanodermic male patient from Angola referred to the Endocrinology department of a central hospital, in Lisbon, Portugal. He presented skeletal deformities and joint laxity, and numerous mucosal neuromas of the oral cavity since early childhood. Recurrent diarrhea was also reported but elevated blood pressure was not observed at that time. Multinodular goiter (nodules $>$ 40 mm) was identified in physical examination and microcalcifications were evident in thyroid ultrasound. Calcitonin and Carcinogenic embryonic antigen levels were 9891 pg/ml and 471 ng/ml, respectively, at the time. Histologic diagnosis of medullary thyroid carcinoma was established after total thyroidectomy, and cervical lymph node resection ensued. Solid adrenal nodules were identified bilaterally in a CT scan, but washout above 60% suggested benignity. Serum methanephrines were three times higher than reference value but MIBG scan and Octreoscan were both not suggestive of pheocromocytoma. The patient remained normotensive until the age of 29. Only then, after repeated MIBG, laparoscopic bilateral adrenalectomy was performed and two solid heterogeneous lesions measuring 16 and 30 mm, on the right and left adrenal glands, respectively, were removed. Histological analysis confirmed 4 benign pheocromocytoma. DNA analysis of the RET gene identified a heterozygous germline mutation: c. 2753T $>$ C (p. Met918Thr). Follow-up CT scan identified *de novo* multiple secondary liver lesions. Current calcitonin and CEA levels are 11217 pg/ml and 179 ng/ml, respectively, and diarrhea is still the main complaint, requiring symptomatic therapy. Herein, we present a case of late MEN 2B diagnosis in order to reinforce the need for a higher awareness of the specific phenotype in order to accomplish the goal of a timely and adequate treatment.

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Poster Presentations: Pituitary and Neuroendocrinology

Adrenal cortex (to include Cushing's)

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Cyclical cushing presented as PCOS in 37 years old lady

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Introduction
PCOS is the most frequent endocrine disorder in women of reproductive age but its diagnosis remains one of the most challenging issues in endocrinology, gynecology, and reproductive medicine. Cyclic Cushing's syndrome (CS) is a rare disorder, characterized by repeated episodes of cortisol excess interspersed by periods of normal cortisol secretion.
History
37 years old lady presented with weight gain for 2 years duration. She has noticed that her weight and hirsutism fluctuated significantly in cycles despite strict dieting and regular exercises, for which she visited many clinics for almost 2 years. She finally diagnosed as a case PCOS. Upon more history taking her weight increased by 20 kilograms mainly trunkal. There was no associated proximal myopathy. She was also complaining from amenorrhoea. There was no easy bruising, or striae.
Diagnosis and Treatment
On presentation BMI was 50 kg/m2 witht marked truncal obesity. Blood pressure was 160/80 mmHg and there were no other clinical stigmata of hypercortisolism. The diagnosis of PCOS was revised and possibility of Cushing's syndrome kept in mind especially in setting high blood pressure and progressive weight-gain. 17-OHP and serum testosterone was normal. 24-hour urinary free cortisol excretion was high at 280 (normal $<$200 nmol/24 h) and overnight dexamethasone suppression test was normal too. These tests repeated after 4 weeks and were normal again. After another 6 weeks, patient continues to complain of more weight gain and appearance of few striae, here the tests repeated and both 24-hour urinary free cortisol and overnight dexamethasone suppression tests were positive (repeated twice) also midnight salivary cortisol level increased. 48 hr low dose Dexamethasone suppression test showed failure of cortisol suppression (Baseline 400 nmol/l; 48 hr 125 nmol/l) confirming endogenous hypercortisolism. High dose DST suppressed cortisol to 49 nmol/l confirming ACTH dependent Cushing Syndrome (ACTH 32 ng/L; normal range 0.1 to 47). Pituitary MRI demonstrated a 12$\times$10 mm adenoma. Transphenoidal pituitary surgery was performed, however patient continue to have hypercortisolism after surgery, then she underwent radiotherapy and she received ketoconazole for controlling her cortisol level which continue to show fluctuations.
Conclusion
Cyclical Cushing Syndrome is a rare entity and often misdiagnosed. Cyclical manifestation of hypercortisolism symptoms and signs are suggestive of the diagnosis and endocrine testing during symptoms will help to reach the diagnosis. A high index of suspicion is crucial for diagnosis.

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Combined cavernous and inferior petrosal sinus sampling in the differential diagnostic of ACTH-dependent Cushing's syndrome

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Purpose
Inferior petrosal sinus sampling (IPSS) is considered the gold standard test for the differential diagnosis of ACTH-dependent Cushing's syndrome, but false-negative results have been reported in 1–10% cases. Cavernous sinus sampling (CSS) was suggested as a diagnostic tool in a complex ACTH-dependent Cushing's syndrome cases.
Aim
To study the role of bilateral combined cavernous and inferior petrosal sinus sampling (BCIPSS) in differential diagnosis of ACTH-dependent Cushing's syndrome.
Materials and methods
34 patients (6 men) mean age 42,2$\pm$12,9(25–67) with ACTH-dependent Cushing's syndrome were included. ACTH-dependent hypercorticism was diagnosed according to generally accepted recommendations. Indications for BCIPSS were: MRI pituitary adenoma size $<$8 mm in 26 cases or absence of pituitary tumor in 8 cases. ACTH CS(IPS)/P ratio$\geq$2 or normalized ACTH/prolactin CS(IPS)/P basal ratio$\geq$0,8 indicated the Cushing disease (CD). Ectopic ACTH-dependent syndrome (EAS) was diagnosed if ACTH CS(IPS)/P ratio was$<$2 or normalized ACTH/prolactin CS/P and IPS/P basal ratio was$<$0,6. All patients underwent surgery (transsphenoidal endoscopic adenomectomy in patients with CD, resection of ectopic ACTH-producing tumor in patients with EAS). Diagnosis CD or EAS was approved by immunohistochemistry and/or clinical improvement (adrenal insufficiency after operation).
Results
In 28 patients ACTH CS(IPS)/P ratio was$\geq$2, that confirmed pituitary origin. Noteworthy, in two patients the data for CD were obtained only by the results of CS sampling, and in four only by the data of the IPS sampling. All patients underwent TSS, CD diagnosis after surgery was confirmed in everyone. In 6 patients ACTH CS(IPS)/P ratio indicated EAS: it was$<$2. But in three of them normalized ACTH/prolactin CS(IPS)/P basal ratio was$\geq$0,8; also, they harbored an adenoma according to pituitary MRI. CD considered confirmed and TSS was performed in these three patients and subsequent IHC study confirmed the ACTH-secreting adenoma. In two patients the normalized ACTH/prolactin CS/P and IPS/P basal ratio was$<$0.6, in one 0.7. A survey to identify the source of ectopic ACTH-production was done. In one case it was pheochromocytoma with ectopic ACTH-secretion and in two cases bronchial carcinoid. All patients were successfully operated on.
Conclusion
According to our data, in the differential diagnostic of ACTH-dependent Cushing's syndrome combined CS and IPS sampling may improve the results and increase the accuracy of the method. In ambiguous cases normalized ACTH/prolactin CS(IPS)/P basal ratio can be effectively used.

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Hair cortisol in adults with Prader-Willi syndrome

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Background
Prader-Willi syndrome (PWS) is a rare genetic, neurodevelopmental disorder. In adults the syndrome is characterized by muscular hypotonia, hyperphagia, increased risk of morbid obesity and behavioral problems. Endocrine insufficiencies are common, although insufficient function of the hypothalamus-pituitary-adrenal (HPA) axis seems to be rare. The effect of long term exposure to cortisol, which is associated with stress and obesity, is unknown in PWS. Measurement of hair cortisol is a convenient, non-invasive method to assess chronic stress.
Aims
To evaluate long-term exposure to cortisol by measurement of hair cortisol and relate levels to BMI and stress
Methods and materials
29 adults PWS patients, 15 men and 14 women, median age 29 years, BMI 27 kg/m^2, participated. A scalp hair sample was collected and analyzed for cortisol concentration. In addition, the patients or their relatives answered questions related to anthropometry and factors potentially influencing hair analysis.
Results
Median hair cortisol was 3.0 pg/mg (range $<$1.3 to 105.6) and mean 95%CI was 12.9 pg/mg (3.7, 22.1). Hair cortisol levels were positively correlated to age and BMI ($P<0.001$ for both). Six patients had elevated cortisol levels, in 5 of them related to significant stressful events.
Conclusion
Hair cortisol concentrations were comparable to upper limit for healthy individuals and long-term stress lead to an increase in hair cortisol. All together our results indicate a normal function of the HPA-axis in this cohort of adults with PWS.

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Absent adrenarche in adults with congenital hypopituitarism

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Background
The mechanisms regulating adrenarche have not been elucidated, although evidence supports a critical role for ACTH and possibly other unidentified pituitary or adrenal contributing factors. Absent adrenarche has been described in children with a variety of sellar tumors. We describe a case series of five adults with congenital hypopituitarism and absent adrenarche.
Cases
Three females and two males with "idiopathic" congenital hypopituitarism, median age 24 years, of which one male and one female were siblings. All patients had GH, gonadotropin and thyrotropin deficiencies and were diagnosed with hypopituitarism in childhood (median age 7). The two male patients opted to restart GH replacement several years after having been treated as children. None had a history of adrenal crisis. All but one female patient were treated with hydrocortisone. The patient not receiving hydrocortisone had subclinical ACTH deficiency, with normal morning ACTH and cortisol levels, but subnormal cortisol peak at 13.9 mcg/dl during an insulin tolerance test. One male patient had developed full body hair following consistent testosterone replacement since puberty, while the other male started developing axillary and pubic hair following re-institution of, and adherence to testosterone replacement. Associated abnormalities noted: the patients had skin dryness of various degrees and puffy hands and feet. One male was diagnosed with lichen planopilaris by skin biopsy taken from the scalp and had significant lymphedema at the lower extremities, one female has isolated dextrocardia, psoriasis and vitiligo. The two affected siblings have sinus bradycardia with a resting rate of 45 bpm; their unaffected brother also has sinus bradycardia. All patients had frankly low age and sex-adjusted serum levels of dehydroepiandrosterone sulphate (DHEAS).
Conclusions
This likely heterogenous group of adults with congenital hypopituitarism failed to demonstrate adrenarche. Androgen-dependent hair appeared only after testosterone replacement in the males. Genetic and metabolomic profiling is needed to enhance understanding of the interplay between pituitary hormonal stimuli, the intra-adrenal environment and even the specific follicle characteristics underlying the process of adrenarche.

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Clinical case reports – Pituitary/Adrenal

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Abstract withdrawn.

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Prolonged QT intervals in a patient with empty sella and isolated ACTH deficiency.

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Introduction
Adrenal crisis is a life-threatening emergency, however, the relation between adrenal crisis and life-threatening arrhythmia is not known. We describe the case of a patient with adrenal crisis and arrhythmia with prolongation of QT interval.
Case report
A 56-year-old woman was admitted to our hospital because of syncope. She reported having had similar episodes in the last year. She had no previous diagnoses and was not receiving any treatment. She presented at the emergency department with new episodes of syncope and depressed level of consciousness. The ECG strip showed prolongation of QT interval and the ECG monitoring registered polymorphic VT (Torsade de Pointes), so the patient was referred to the intensive care unit. On physical examination, her palpebral conjunctiva was pale, and her skin and her tongue were not pigmented. Routine blood examination revealed hyponatremia (126 mEq/L) and hyperkalemia (5.7 mEq/L) with low glucose levels. Fluid therapy with a dextrose solution was necessary to maintain normal glycemia. She was suspected to have adrenal insufficiency and the cortisol blood level confirmed this diagnosis (0.19 mg/dl). Endocrinological examination revealed normal pituitary function except for very low serum concentrations of ACTH and cortisol. Ultrasound echocardiography showed normal cardiac size and function of the left ventricle. On the basis of this diagnosis, hydrocortisone replacement was started. After hydrocortisone replacement was started, the sodium level returned to normal and the QT intervals of ECG were normalized. Pituitary magnetic resonance imaging showed empty sella.

Laboratory data		Normal range
Na+	126 mEq/L	(136-146)
K+	5.7 mEq/L	(3.5-5.1)
Cortisol	0.19 mg/dl	>18
ACTH	4 pg/ml	(4.7-40)

Conclusion
Long QT syndrome is one of the symptoms of isolated ACTH deficiency and is known to be a risk factor for cardiovascular events. In these patients, prolonged QTs can be reversed by glucocorticoid replacement.

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Delayed puberty vs hipogonadotropic hypogonadism; how long to wait to treat?

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We presented the case of a 21 years old patient, derived from Primary Care to evaluate low testosterone levels (total testosterone (TT) 0.44 ng/ml). His father had delayed pubety and his mother menarche was at 11 years. No other personal history of interest. He had adequate child development and vaccination. No parotiditis. He referred some morning erections. Weight 59 kg, size 171 cm and BMI 20.17 kg/m^2. Testes volume (TV) of 4-5 cc, scanty pubic hair. Tanner stage 1-2. No dysmorphic features. We repeated blood test: TT 0.20 ng/ml, sex hormone binding protein (SHBG) 89.8 nmol/l, follicule stimulation hormone (FSH) and lutein hormone (LH) inappropriately low. He had normal basal pituitary hormones. His bone age was according. Testicular and abdomen ultrasound were normal and karyotype was 46XY.Pituitary MRI showed normal hyphofysis. Smell test showed no alteration. We proposed a differential diagnosis between delayed puberty or hypogonadotropic hypogonadism. We started treatment with low doses of human chorionic gonadotropin (HCG), 1000 ui 3 days a week. After 3 months of treatment, he had TV 8-10 cc, greater development of secondary sexual characteristics. TT 8.57 ng/ml, SHBG 52.7 nmol/l. Treatment was maintained six months. At that time he had TV of 10-12 cc, greater development of total muscle mass. TT 4.19 ng/ml, SHBG 39.1 nmol/l. Spermiogram persisted in cryptospornozoospermia hypospermia. According to TT levels we suspended HCG treatment and schedule a blood test control to assess testosterone levels without stimulation. After 3 months without any medication TT levels had decreased again below normal range (1.25 ng/ml).

This fact guided us towards the need for definitive treatment with testosterone. We started replacement with low dose of cypionate testosterone and progressive increase. Currently he had good testosterone levels with the substitution treatment. Genetic study for possible mutations had showed a variant in heterozygosis described as of uncertain clinical significance c.566G>A (p.Arg189His) in the FGFR1 gene. The study made to his parents showed that his mother is a carrier of the same variant. To date and due to the lack of evidence linking this variant with pathology to be inherited from an apparently healthy parent, it is probably an inherited polymorphism. It should be noted that the existing bibliography recommends reanalyzing the existence of a less defined phenotype of the parent carrier to rule out causality. This study does not rule out the genetic origin of the process or the consequent risk of repetition.

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Isolated secondary adrenal insufficiency associated with primary hypothyroidism presenting with hypoglycemic coma

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A 27-years old man admitted unconscious due to severe hypoglycemia of 18 mg/dl with right-sided hemiparesis and hypotension. There was a several months history of tiredness and weight loss. Past medical history was remarkable for traumatic brain injury after unexplained syncope, primary hypothyroidism and an episode of hypoglycemia of 2 mmol/l with total improvement after iv infusion of glucose(five months previously). There was no history of drug or alcohol intake. He was on levothyroxine replacement therapy at the dosage of 75 mcg. He appeared lean (weight 58 kg, height 185 cm). There was no abnormal skin or mucosal pigmentation and secondary sexual characteristics were normal. His laboratory findings of TSH 20.35 μIU/l (0.2–4.2), free T4 3.7 ng/L (8.0–17.0), cortisol 2 ug/l (45–260) and plasma ACTH 1.7 ng/l (7.2–63.3) were consistent with adrenal insufficiency and uncompensated hypothyroidism. Abdominal CT-scan showed normal adrenal glands and cholelithiasis. During MRI of the brain pathology of the hypothalamus-pituitary region was excluded. He showed quick improvement after iv infusion of glucose and hydrocortisone with complete resolution of right-sided hemiparesis in two weeks. One month after he re-admitted for evaluation the hypothalamic-pituitary-adrenal axis. Basal morning hormone levels suggested secondary adrenal deficiency without other significant changes in pituitary and islet-cells function: cortisol <28 nmol/l (119–618), ACTH <1.1 pmol/l (0–10.2), TSH 15.5 μIU/l (0.4–4.0), free T4 18.6 pmol/l (11.5–23.2), insulin 11.6 mIU/l (5.0–25.0), C-peptid 0.73 nmol/l (0.5–2.5), LH 3.6 IU/l (0.6–12.0), FSH 7.28 IU/l (1.0–12.0), total testosterone 10.4 nmol/l (3–12), GH 0.4 μIU/l (0.16–13.0), IGF1 238 ng/ml (117–329), prolactin 548.6 mcIU/ml (40–390). After insulin-induced hypoglycemia there was an absence of cortisol and ACTH increase – cortisol remained <27.6 nmol/l (119–618) and ACTH <1.1 pmol/l (0–10.2) at the glucose level of 20 mg/dl on the 50th minute. There were no growth hormone changes of clinical significance in the test. These results confirmed isolated ACTH deficiency whereas hyperinsulinism and other causes of hypoglycemia and syncope were excluded. Patient discharged on hydrocortisone 25 mg and levothyroxine 100 mcg per day. During a year follow-up there were no episodes of hypoglycemia and fatigue.

Conclusion

This case shows the importance of timely investigation of episodes of hypoglycemia of unclear origin in patients with existent autoimmune disorders to exclude secondary adrenal insufficiency.

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Clinical case of exogenous Cushing Syndrome during injections and on topical glucocorticoids

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Background

Topical glucocorticoids (GCS) are seems to have low percent of adverse effects (AE). However, inappropriate use led to AE.

Material and methods

One patient with psoriasis received topical GCS (clobetasol), one patient with coxarthrosis - steroid injections (diprospan).

Cases

Woman A., 32 y.o., applied topical GCS (clobetasol) for 9 weeks for psoriasis. Area of application – abdomen and elbows. Frequency of application – daily, one tube. Three weeks after the beginning of the above therapy, she noted a proximal muscle weakness, facial plethora, striae (purple, 1.5 cm wide), weight gain (3 kg). Oral glucose tolerance test (OGTT) revealed impaired glucose tolerance (IGT). ACTH and UFC were low. It took 1.5 months for restore of pituitary-adrenal axis. Man O., 57 y.o, made by themselves injections of diprospan (1 ml/5 mg) once a week for 12 months to treat coxarthrosis. After 3 months of such therapy a proximal muscle weakness, facial plethora, striae (purple, 2.0 cm wide) occurred. Ten months after the beginning of above therapy, he noted an acute pain in his back. On MRI – compressive vertebral fractures of Th6, 11, 12, L3. On DEXA – osteoporosis. Laboratory evaluation 7 days after last injection: deficiency of vitamin D, ACTH – 5.3 pg/ml (7.2–63.6 pg/ml), serum cortisol – 1.0 mkg/dl (6.2–19.4 mkg/dl), normal level of calcium. Now he has secondary adrenal insufficiency.

Conclusion

Topical GCS in large doses can cause secondary adrenal insufficiency. Uncontrolled GCS injections lead to severe adverse effects.

Keywords: glucocorticoids, hypercorticism, facial plethora, weight gain, striae, Crushing's syndrome

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An acromegaly case; presented from pituitary apoplexia to overt acromegaly before diagnosis

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Pituitary adenomas are the most common lesions of sellar cavity. The usual symptoms are associated with endocrine dysfunctions and mass effects. In this case, a 39 year old female presented with headache for one year and progressive blurred vision, nausea, vomiting for two days. Brain magnetic resonance imaging showed a 16×9 mm hemorrhagic macroadenoma in sellar cavity concordant with apoplexia and anterior pituitary hormone deficiency. The patient underwent transshphenoidal surgery and necrotic, heterogeneous hemorrhagic adenoma was excised. Pathology showed extensive coagulation necrosis and hemosiderin pigments therefore immunohistochemical staining could not be performed. After her admission to our clinic there were no typical features suggesting acromegaly or Cushing's disease and postoperative anterior pituitary hormone deficiency has not been recovered as well as insulin like growth factor 1 (IGF1) levels. Hence, she was put on hormone replacement therapy for desmopressin, levothyroxine, hydrocortisone, estrogen and progesterone. After 5-years of follow up period, some clinical features such as; enlargement of hands and feet, macroglossia and maloclusion in teeth were noticed. Subsequent investigations showed moderately elevated serum growth hormone (GH) (7.39 ng/ml) and IGF1 levels (553.4 ng/ml). An oral glucose tolerance test was perfomed and nadir GH level was 2 ng/ml. Pituitary MRI revealed a recurrent pituitary adenoma 25×16×19 mm in size without invasion to adjacent structures. The patient was diagnosed as recurrent GH secreting pituitary adenoma which had been cured by apoplexia before. Transshphenoidal surgery was performed for adenomectomy and the pathology confirmed the diagnosis. Ki-67 proliferation index was very high as 20% and p53 was immunoreactive, which predicted an agressive tumor. As GH and IGF1 levels were still elevated at the third month of surgery she was put on lanreotide LAR 90 mg/28 day. The dose was titrated to 120 mg/28 day as we could not achieve controlled disease. Although there were no visible residual tumor on postoperative MRI, the disease was uncontrolled even though cabergoline addition. Disease control was achieved on the 6. months of gamma-knife therapy. The clinical signs of hormonal hypersecretion might regress in case of apoplexia, therefore the clinicians should always be alert for reappearance of the disease on follow-up. This case also underscores the higher Ki-67 index and extensive p53 immunoreactivity which might be seen in recurrent cases after apoplexia.

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Acute hyponatraemia complicating therapy of acute hepatic porphyria need immediate correction before become symptomatic: a case report

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Introduction
Acute hepatic porphyria is a relatively rare metabolic disorder. Its typical clinical manifeastations are abdominal symptoms and/or troubles belonging to the cerebral oedema. Clinical picture of acute abdomen is frequent and unsuccessful surgical treatment leads to the diagnosis of porphyria.
Case description
Female, born in 1987, presented in emergency surgical unit as appendictis. She was operated but the problems did not disappear. After 3 days, the patient was readmitted with abdominal pain, vomiting and lack of wind and stools, weaknesses. The urine was reddish and at the end porfobilinogen in urine was confirmed.The day before the admittance to the hospital sodium level was 134 mmol/l and on the day of admittance 128 mmol/l. Therapy with 1000 ml 5% glucosae and 1000 ml Ringer solution was administered. Tommorow morning, the patient was with similar troubles but her Na was 116 mmol/l. She was considered to be acute asymptomatic hyponatraemia. 10% glucose solution plus 20 ml 50% glucose was continued plus 0.9% NaCl.The next morning she started to feel bowel movements and since one week ago she started to feel better. However, suddenly patient developed seizures, with foam on mouth, circulatory collaps and respiratory arrhest. Na at that moment was 113 mmol/l. Patient was successfully reanimated. That day received 10 g/24 h od sodium chloide and only 3g as 'bolus'. On that therapy tomorrow morning Na was almost unchanged, as it was the case during the whole previous day (110–116 mmol/l). So we decided to give 3g NaCl (125 ml of 3% SolNaCl) on 2–3 h, a total of 12 g. during the day and Na raised to 120 mmol/l, with desired +7 mmol/l rise per day. Next day Na was 130 mmol/l with the need of only one dose of 3 g NaCl. We confirmed acute hepatic porphyria by porphobilinogen of 67, uroporphyrin 455 and coproporhyrin 1333 mmol/l in urine. During the treatment pottassiium level was between 3.1–3.5 mmol/l.
Discussion
The aim of this case report is to emphasize the importance of rapid correction of acute hyponatriaemia, whatever its cause is. Sodium incerase have to be not more than 10 mmol/l/24 h. We do not have to wait hyponatraemia symptomaticity as it was in our case report. As we are affraid of cardiac arrhythmias in case od low potassium, we shoud escape raised intracranial pressure symptomts of low sodium. Patients syster, also with porphyria, died suddenly when she was 20 y. old.

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Pasireotide a new option for acromegaly

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Background
Acromegaly is a rare neuroendocrine disorder caused by secretion of excessive levels of growth hormone. Somatostatin receptor ligands (SRLs) are first-line medical therapies for patients in whom surgery has failed or is contraindicated. We report a case who had inadequate response to multiple therapies including surgery,radiotherapy,octreotide,lanreotide,cabergoline and pegvisomant.
Case
An 44-year-old woman was admitted to our hospital with a past medical history of acromegaly diagnosed 6 months ago. Initially she was treated with transcranial surgery for a 3 cm hypophyseal macroadenoma. She was given steroid and L-thyroxin replacement therapy after surgery. Physical examination revealed an overweight female patient with enlarged nose,lips,coarse facial features, macroglossia and enlargement of both hands. She had been receiving lanreotide for 6 months. Serum growth hormone (GH) and IGF1 levels were 6.66 ng/ml and 1291 ng/ml respectively**.** MRI(Magnetic Resonance Imaging) showed a 1.5 cm and a 1.2 cm residual tumors with suprasellar extension and optic nerve traction. Bitemporal hemianopsia was present on visual field examination. Serum GH and IGF1 levels were 40 ng/ml and 3985 ng/ml preoperatively. In the course of the disease,persistent elevated GH and IGF1 levels were observed. Tumour debulking is not recommended because of the cavernous sinus involvement. Two years after surgery, 180 gy conventional radiotherapy was performed because of inadequate response to medical therapy. In the course of the disease medication was modified as follows: Lanreotide switched to octreotide, combined with cabergoline. 2 years later, pegvisomant was started at initial dosage of 10 mg/day then titrated. During this medication, eventhough a slight decrease was observed, IGF1 levels were stil high. Despite these regimens, the biochemical markers were stil elevated,visual field defects were stil present and MRI revealed no significant change in residues. 1.5 years later, all medications were stopped and pasireotide was started with dosage of 0.6 mg/s.c./daily. Within 3 months after pasireotide treatment, a significant decrease was observed on GH an IGF1 levels. At the end of 6 years,biochemical remission was achieved. For diabetes management she used insulin but after biochemical control, insulin was stopped and GLP-1 receptor agonists were given. Her blood glucose levels were normal with this medication.
Conclusion
Pasireotide is a multireceptor-targeted SRLs. It seems to be a proper medical option for treatment of severe acromegaly cases who are resistant to other SRLs.

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Diabetes insipidus as first clinical manifestation of pineal tumor

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Introduction
Central diabetes insipidus is a disorder characterized by polyuria and polydipsia due to vasopressin deficiency caused by a lesion at the hypothalamo-hypophyseal axis. Frequently, central diabetes insipidus is wrongly considered idiopathic if not associated with other neurological signs and symptoms. Herein we present the report of a case that illustrates the difficulties in the diagnosis of this condition.
Case report
A 17 year-old male was admitted to our hospital with history of polydipsia, polyuria, and nocturia for 2 months with no neurological symptoms. These clinical manifestations characterized the presence of diabetes insipidus, so performance of a water deprivation test was indicated: after a 4-hour fasting period, there was increase in the plasma concentration with no increase in urinary concentration; 1 hour after the stimulus with desmopressin, there was an evident increase in urinary osmolality. Thus, we confirmed the presence of central diabetes insipidus, and therapy with desmopressin was initiated. We completed the study with a magnetic resonance that showed 'Pituitary stalk with nodularity in its most cranial portion and iso-intense with respect to the adjacent parenchyma'. Considering the radiological and clinical findings and the absence of abnormality in the pituitary hormonal study, initial diagnosis was idiopathic central diabetes insipidus, nevertheless a close follow up of pituitary nodularity described would be done. Two months later, our patient referred frontal headache associated with nausea and vomiting, so a new magnetic resonance was performed. Imaging showed 'a mass in the pineal region (18×18×19 mm) causing obstruction of the aqueduct of Silvio, with acute obstructive hydrocephalus data'. The most probable diagnostic hypothesis was pineal tumor; among these tumors, germinoma is the most common histological type and it was confirmed with a biopsy. Serum levels of alpha-fetoprotein and HCG were measured, with high level results for HCG. Radiotherapy was indicated, and it was performed with an initial satisfactory clinical and imaging response. However, our patient currently is receiving chemotherapy because of leptomeningeal tumor dissemination.
Conclusions
Our case report shows the difficulties in the diagnosis of tumors at the pineal region. Germinomas may have central diabetes insipidus as their first

manifestation. The symptoms of diabetes insipidus may precede the alterations in the magnetic resonance. Whenever diabetes insipidus is present, we should perform a complete study, considering that the presence of these tumors cannot be discarded, even in cases of an initially normal neurological examination.

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P699

Acromegaly and subclinical Cushing's disease: a rare case of a pituitary macroadenoma secreting both GH and ACTH

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Introduction
Plurihormonal pituitary adenomas are unusual tumors which typically belong to one cell lineage and have an incidence of approximately 1.3%, the most common combination being GH, PRL and glycoprotein hormone subunits. There are a few cases in the literature describing cosecretion of GH and ACTH from a pituitary adenoma, the incriminated pathogenesis being the origin from different cell lineages and the aberrant patterns of transcription factors.
Case report
We report the case of a 49 years-old male patient who accused headaches and elevated arterial blood pressure. Physical examination showed a fully developed acromegaly, multiple papillomas and a lipoma, with no cushingoid features. Pituitary investigations revealed hypersecretion of both somatotrophic and corticotrophic axes and the MRI described a pituitary macroadenoma with compressive effects on the pituitary stalk and the optic chiasm. He underwent transsphenoidal surgery. The immunohistochemical staining confirmed the GH secretion with minimal expression of ACTH, PRL, TSH and relatively reduced proliferative activity (Ki67-7%). Postoperative follow-up revealed a tumoral rest with persistent hypersecretion of GH and ACTH, with no inhibition at low dose of dexamethasone. We obtained control of the acromegaly under somatostatine analogs and cabergoline, while for the corticotrophic component of the tumor, we considered appropriate in this case stereotactic radiotherapy. The patient currently is in observation regarding the effect of this therapy.
Conclusions
We describe an uncommon case of a mixt secretion of GH and ACTH from a pituitary macroadenoma; while we controlled the somatotrophic component, concerning the ACTH hypersecretion, we will take into consideration treatment with pasireotide in case of inefficiency of the Gamma-knife surgery.

Keywords: Pituitary adenoma, Growth hormone, Adrenocorticotropic hormone.
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P700

Hypogonadism following high-voltage electrical brain injury

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Introduction
Male hypogonadotropic hypogonadism (HH) is a consequence of congenital or acquired diseases that affect the hypothalamus or the pituitary gland. In HH, secretion of gonadotropin releasing hormone (GnRH) is absent or inadequate. Diagnosis during adulthood (after normal puberty) suggests an acquired etiology. Acquired hypogonadotropic hypogonadism can be caused by drugs, infectious or infiltrative lesions, systemic diseases, radiation and TBI. Post-TBI neuroendocrine disorders have been increasingly acknowledged in recent years, especially related to road accidents, sports or falls. The frequency of hypopituitarism after TBI varies between 15-50% among different studies. Hypopituitarism can be complete (panhypopituitarism) or parcial (isolated deficiency). GH is the most common hormone lost after TBI, followed by ACTH, gonadotropins (FSH and LH), and TSH.
Case study
Man, 38, a member of the Air Force Rescue Squadrons, single, with a 7-year-old son, presents with asthenia, insomnia, decreased libido and difficulty in erection in early 2015. Blood tests revealed a low testosterone level, with gonadotropins in the normal range, suggestive of central hypogonadism. An evaluation of the pituitary axis was performed and cleared and an imaging study with MRI-CE did not report space occupying lesions (SOL). In the etiological evaluation for hypogonadism there is a history of orchidopexy, with a decrease in testis at the age of 8. Also, a work accident in late 2014 with electrocussion without apparent sequels. He is currently being medicated with testosterone IM 3/3 months with strong clinical and analytical improvement.
Discussion
The causes of acquired hypogonadotropic hypogonadism are multiple. In our patient we could not find any obvious etiology. There was no history of trauma, infection, systemic illnesses and he denied drug abuse. The MRI excluded the presence of any SOL. The only apparent insult to our patient's pituitary was therefore electrical brain injury. Several authors have found similarities between victims of electrical injuries and of head trauma, although the mechanism of lesion is still uncertain. Given the temporal relationship between the work accident and the beginning of the symptoms (about 6 months), it was hypothesized that HH could be a deficit resulting from high-voltage electrical brain injury. We found no similar cases reported in the literature, therefore only time will tell if the condition may be reversible. Hormonal replacement therapy may reduce morbidity, optimize rehabilitation and improve the quality of life of the patients.

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P701

A case of hypothalamic-pituitary disease: who's the deceiving suspect?

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Introduction
Diagnosis and treatment of neurosarcoidosis (NS) can be challenging. We describe an unsual presentation of an isolated NS in a 21 year old adult, initially presenting with central diabetes insipidus (DI) associated with a stalk thickening at the age of 14.
Case description
A 21 year old patient was first seen at the department of endocrinology after a 9 years follow-up for panhypopituitarism. He presented at the age of 14 years at the pediatric endocrinology clinic with a central DI, related to a lymphocytic infundulonеurohypophysitis. In the following years, he developed a panhypopituitarism, which was correctly substitued. Yearly MRI of the brain showed no changes of the anterior pituitary and a stable aspect of the infiltration of the stalk for almost 3 years after the initial diagnosis. At transition to adult endocrinology clinic, MRI re-evaluation for headache showed however an extension of the lesion to suprasellar with an involvement of the optic chiasm. A lumbar puncture showed lymphocytic pleiocytosis and elevated protein level, whereas beta-HCG and alpho-fetoprotein were negative. A chest CT only showed few mediastinal adenopathies. An elevated serum angiotension converting enzyme level was documented, whereas antinuclear antibodies and antineutrophil cytoplasmatic antibodies were negative. He was treated empirically with corticosteroids 0.5 mg/kg based on the clinical diagnosis of NS. Three months later, an aggravation of the visual defect in the left eye with a significant increase in the volume of the suprasellar mass on MRI was documented. Furthermore, he developed a Cushing syndrome related to the corticotherapy. Since the corticotherapy did not ameliorate neither the clinical nor the radiological features, a stereotactic brain biopsy was planned. The biopsy showed a granulomatous inflammation, compatible with NS. He was subsequently treated with 3 pulse doses 1gr solumedrol and was started on mycophenolate mofetil 1 g 2x/day. He received in parallel a treatment with low dose radiotherapy. A control MRI of the brain 2 months later, showed a nearly complete involution of the contrast enhancing lesion, but an unchanged thickening of the optic chiasm. MMF was given for 12 months.

Conclusion
Isolated NS is rare in children. This case report is exceptional because of the lag time of almost 9 years between initial symptoms and the finding of an evolutive infiltrative lesion to suprasellar. NS can be the only manifestation of an underlying systemic sarcoidosis, and although good response to corticosteroids in general, addition of other immunomodulators may be necessary.

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Cyclic Cushing's syndrome: a difficult diagnosis

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Introduction
Cyclic Cushing's syndrome (CS) is a rare disorder characterized by repeated episodes of cortisol excess interspersed by periods of normal cortisol secretion. These phases may range from days to years. The diagnosis is a difficult challenge.
Case report
We present a case of 56-year-old women with hyperglycemia, hypertension, central obesity, edema, bruising, fatigue and emotional lability for several years. Laboratory tests: glucose 141, HbA1c 11%, LDL-cholesterol 121, HDL-cholesterol 84, triglycerides 95, Na 143 and K 3.3, 24-hour urinary free cortisol 662 µg (4.3–176), cortisol rhythm with basal serum cortisol 9 h 8.5 and 21 h 24 µg/dl, 1-mg overnight dexametasone suppression test revealed a morning serum cortisol concentration of 18.6 µg/dl (<1.8), ACTH 75 pg/ml (5–50) and 8-mg overnight suppression test pointed a pretreatment morning serum cortisol 30.1 which was suppressed to 6.8 µg/dl (71%). Pituitary magnetic resonance was normal. Inferior petrosal sinus sampling (IPSS) was ordered but it was cancelled because clinical and biochemical hypercortisolism disappeared. Three months later, hypercortisolism appeared and immediately IPSS was made. IPSS was diagnosis of a central source for ACTH secretion. The patient was treated successfully with transsphenoidal hypophysectomy. Histopathology revealed a 4.5 mm pituitary corticotroph microadenoma. After that, there were normalization of the hypercortisolism and the phenotype but hypopituitarism was established.
Conclusions
The diagnosis of cyclic CS is difficult to make given the variations in clinical presentation, the unpredictability of cyclic secretion and the lack of uniformity in etiology. Causes of cyclic CS are multiple dominated by pituitary adenoma. Patients can have periods of clinical improvement during these quiescent phases or remain symptomatic. IPSS should be made only when biochemical hypercortisolism is present at the same time.

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P703

A rare cause of central hypothyroidism: oral isotretinoin treatment

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Background
Isotretinoin has been used for many years to treat moderate or severe nodulocystic acne, disorders of sebaceous gland and keratinization and in the prevention of skin cancer. Certain types of retinoids may cause abnormalities in serum thyroid function tests by suppressing thyroid stimulating hormone (TSH). However, it is uncertain whether systemic isotretinoin has any effect on thyroid functions.
Case
18 years old woman has admitted to our hospital complaints of fatigue and drowsiness. She has no known systemic disease. At the dermatology clinic, she was prescribed isotretinoin (30 mg/day) for the treatment of severe acne. At the 3rd month of the treatment, laboratory tests revealed decreased sT4: 0.74 ng/dl (normal range: 0.89–1.37), sT3: 1.92 pg/ml (normal range: 2.25–3.85), and TSH: 0.023 µIU/ml (normal range: 0.47–3.41) levels. All other pituitary hormone levels were analyzed and found to be at normal blood values. Since the magnetic resonance imaging of the pituitary gland was reported as normal by the radiology department, the central hypothyroidism of the patient was thought to be related to the medication she was receiving for acne treatment. The isotretinoin was planned to discontinue and levothyroxine was also started for thyroid hormone replacement therapy. By the end of the 2-week levothyroxine treatment, blood hormone levels were determined as st3: 2.95 ng/dl, st4: 0.95 ng/dl and TSH: 1.133 µIU/ml. The patient's symptoms improved after the levothyroxine treatment.
Conclusion
Although central hypothyroidism has not been shown to be clearly associated with isotretinoin therapy, it has been suggested that central hypothyroidism in our patient related with isotretinoin treatment. Therefore, we recommend that patients receiving isotretinoin therapy should be evaluated symptoms of hypothyroidism and performed thyroid function tests.

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P704

The complexity of management of persistent acromegaly from repeated surgical interventions and multiple medical therapies

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Acromegaly prevalence is 2.8–13.7 cases per 100,000. Diagnosis at the early stages can be quite challenging and management is complex involving various specialties to achieve remission of the condition. September 2013, 49 year old lady presented to optometry with few months of bumping into things. She was later found to have superior bitemporal hemianopia. She later described having to change her wedding rings multiple times over the past year with increase in size of shoes. 3 months after presentation, January 2014, diagnosis of acromegaly was made with IGF-1 level of 90.7 nmol/l (4–29 nmol/l) and nadir growth hormone level of 19.3 pg/l. Urgent MRI visualised 2.5*2.4 cm pituitary adenoma with suprasellar extension. A month later she underwent transphenoidal debulking. Histology stained very strongly for growth hormone. Post operative scan showed good tumour bulk reduction and two areas of residual tissue, one posteriorly and the other close to the cavernous sinus. Post-surgically bilateral hemianopia showed marked improvement. Patient was started on 60 mg Lanreotide. After a month due to lack of response this was increased to 90 mg. Medication was eventually stopped after 3 months due to nausea, abdominal discomfort, diarrhoea and later on muscle twitches. Methionine-PET scan showed clear focus within the pituitary that was likely to be the source of ongoing excess growth hormone production. Second debulking operation was done April 2016. IGF-1 stayed constant between July and Septemper of 2016 at 105.4 nmol/l. Patient underwent 5 week radiotherapy early 2017. Lanreotide was re-trialled and stopped due to itching and twitching. Cabergoline was used next and echocardiography follow up showed no evidence of valvular dysfunction. Cabergoline dose was increased and she had side effects which led to it being stopped (nausea drowsiness 24 hours after each dose). Patient was commenced on Pegvisomant and IGF-1 levels fell from 94 to 35 nmol/l; currently on an increased dose of Pegvisomant from 10 to 15 mg SC due to slight increase of IGF-1 levels from 35 to 43 nmol/l.
Conclusion
Management of acromegaly is complex and requires extensive input from both surgical and medical specialties. Debulking is successful in 74% of patients with macroadenoma. Medical therapies can include Somatostatin analogues, cabergoline, octreotide and at last resort pegvisomant. Multidisciplinary approach is essential for remission of the condition with long term monitoring for co-morbidities, notably cardiovascular outcomes.

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P705

A case of hypopituitarism due to acute invasive fungal rhinosinusitis

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Background
Acute invasive fungal rhinosinusitis (AIFR) is a rare but fatal infection that occurs primarily in immunocompromized individuals. It is characterized by fungal invasion into the mucosa and submucosal structures of the paranasal sinuses with extension into adjacent structures, including the paranasal soft tissues, orbit and cranial vault. We present here a case of hypopituitarism due to AIFR with intracranial lesion.
Case
A 59-year-old man, whose past medical history were total gastrectomy due to gastric carcinoma and cerebral hemorrhage, appeared general fatigue. He was diagnosed as hyponatremia due to unknown origin and transferred to our hospital for further examinations. He presented body weight los, right eyelid ptosis and ocular movement disorder. Laboratory data showed severe hyponatremia (Na 119 mEq/ml) and hypopituitarism (ACTH 8.8 pg/ml, Cortisol 4.3 μg/dl, TSH 1.1 μIU/ml, fT_4 0.38 ng/dl) confirmed by endocrinological examinations, on the other hand, b-D-glucan was normal range (9.3 pg/ml). Brain MRI showed an intracranial mass lesion of irregular form at right cavernous sinus and sphenoidal sinus, which considered as culprit lesion of right eye symptoms. A stenosis of right internal carotid artery was also observed, and it progressed to complete obstruction later. Nasal endoscopy revealed a fungal ball at sphenoidal sinus and Aspergillus Fumigatus was detected by culture. Overall, he was diagnosed as hypopituitarism, oculomotor nerve palsy and obstruction of right internal carotid artery due to AIFR. Antifungal agents (VRCZ, MCFG) and hormone replacement therapy (hydrocortisone, LT_4) were started, and then general fatigue, hyponatremia, and eyelid ptosis were gradually improved.
Conclusion
AIFR is usually diagnosed and treated by otolaryngologist, and there are seldom reports on hypopituitarism due to AIFR as the present case. It should be considered AIFR is one of the differential diagnoses in a patient who appears hypopituitarism and/or cranial nerve disturbances, although AIFR with cranial invasion is extremely rare.

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An unexpected cause of severe hypokalemia

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Background
Although the most common causes of hypokalemia are diuretic use and gastrointestinal losses, elevated cortisol levels can also cause hypokalemia through its effects on the renin-angiotensin-aldosterone system.
Case report
A 56-year-old woman with a history of diabetes mellitus and hypertension, presented to our emergency department with fast progressing generalized weakness, abdominal discomfort and diarrhea. Digestive tract diseases were ruled out. Physical examination revealed a female with hyperpigmented face, buffalo neck, and thin upper and lower extremities. She had neither abdominal striae nor moon face. Electrocardiogram (ECG) showed a regular sinus rhythm with diffuse flat T-waves. Laboratory tests indicated hyperglycemia, metabolic alkalosis, thrombocytopenia (15,000 elt/mm^3) and persistent severe hypokalemia (up to 1.9 mmol/l) despite the intravenous infusion of potassium. Markedly elevated plasma ACTH (1782 ng/ml (VN: 10–48)) and cortisol (1340 nmol/l (VN: 200–600)) levels were observed. No suppression of serum cortisol level with high-dose dexamethasone test was found, confirming ectopic ACTH dependent cushing's syndrome (ECS). Chest X ray was normal. Computed tomographic (CT) scan detected a large mass of 53*27*25 mm at the corporo-caudal portion of the pancreas with multiple hepatic and peritoneal metastases. The severe metabolic alkalosis secondary to glucocorticoid-induced excessive mineralocorticoid activity was treated with potassium supplements and spironolactone. A CT-guided biopsy of the mass to determine her pathological type could not be done because of the severe thrombocytopenia. The bone marrow aspiration had not shown metastases. Further investigations havenot been done because of the rapidly fatal evolution.
Conclusion
This case illustrated a rare cause of Cushing's syndrome, ectopic ACTH secretion. A quarter of these cases remain occult without determining the source of the ectopic secretion. They generally present with electrolyte disturbances rather than typical cushingoid feature because the hypercortisolism is an acute phenomenon and the patients generally do not survive long enough until morphologic changes occur.

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P707

Atypical pituitary adenoma: a case of histological mimicry

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We present the case of a 67-year-old man who presented to the outpatient clinic for endocrinological evaluation after partial resection of an atypical pituitary adenoma (APA). Pathohistological assessment of two independent and experienced neuropathologists resulted in a diagnosis of APA with unusually high proliferation indices (Ki67 10–20%/p53 30%) and immunoreactivity for LH, FSH and the alpha-subunit. Clinical examination as well as laboratory testing revealed no significant pathologies, particularly with regard to the pituitary function. This was also true at the follow-up examination 6 month later, after the patient received adjuvant radiotherapy. Another 8 month later the patient presented in a markedly deteriorated state with fatigue and chronic pain syndrome due to multiple vertebral body fractures. Medical workup revealed the diagnosis of a stage III (International Staging System) IgG-kappa type multiple myeloma. With knowledge of the underlying disease the neuropathological examinations were repeated and immunohistochemical staining with antibodies to CD138, CD38 and kappa light chains confirmed pituitary manifestation of the multiple myeloma, although positive staining for LH, FSH and the alpha-subunit was present. On the basis of these findings 138 classical histological specimens of multiple myelomas were examined regarding to gonadotropin and alpha-subunit expression: 2 and 3 tumors expressed LH and FSH, respectively, and nuclear and cytoplasmatic staining of the alpha-subunit was present in a multitude of cases. Most likely, unspecific binding of the used antibodies caused the positive staining. However, in the presented case, this phenomenon supported the initial diagnosis auf APA. This case illustrates that extraosseous manifestation of a multiple myeloma should be considered in cases of APA with high proliferation indices.

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P708

Bromocriptine for management of a patient with cranipharyngioma and central hyperthermia after neurosurgery: a case report

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Introduction
Central hyperthermia is frequent in patients with brain injury and is characterized by a rapid onset with high temperatures, marked temperature fluctuations and poor response to antipyretics. It is associated with worse outcomes in the injured brain, thus it is important to aggressively manage it.
Case-report
We report a case of a 9-year-old boy diagnosed with sellar and suprasellar adamantimomatous craniopharyngioma at the age of 5 when he underwent quasitotal resection. After neurosurgery he developed panhypopituitarism and he received replacement hormonal therapy. Notably, the growth rate was one over expectations of about 7 cm/year despite the somatotropic pituitary insufficiency. The evolution was favorable for 4 years when the MRI scan detects tumor recurrence in the third ventricle that required neurosurgery. He was admitted to

the Iaşi Endocrinology Department following the quasitotal resection of the recurrent craniopharyngioma. During his admission he developed intractable fever which persisted despite antipyretics. A complete fever workup was performed, but no definite infection source was found. Central fever was a result of damage or dysfunction to central fever control centers, such as at the level of the diencephalon. Bromocriptine was started resulting in control of central hyperthermia. A week later the fever did not exceed 38°C and the month following the treatment the body temperature baseline was reduced to 37°C.
Conclusions
We reported a case of prolonged central fever after neurosurgery of a recurrent craniopharyngioma in a child who was successfully treated with bromocriptine. Althought he developed panhypopituitarism after neurosurgery, he associated normal growth rates and growth hormone therapy was not need.
Keywords: bromocriptine, central hyperthermia, craniopharyngioma.
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P709

Successful management of Cushing's disease in pregnancy: a case report

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Introduction
Cushing's disease (CD) frequently leads to hypogonadotropic hypogonadism by hypercortisolism and hyperandrogenemia. In the literature, there are totally 96 cases of CD and pregnancy. Only four of 11 cases, operated transsphenoidally, were cured. We aimed to present a case of CD developing pregnancy in which hypercortisolism was successfully controlled by transsphenoidal surgery (TSS) in 2nd trimester.
Case report
28 years old female was admitted with complaints of not able to lose weight after delivery and hirsutism. She had diagnosis of ALL 9 years ago and two operations because of avascular femoral necrosis. Physical examination revealed supraclavicular fat deposition, purple stria on abdomen, ecchymotic lesions on skin,diffuse hyerpigmentation on back and hirsutism. BMI was 33 kg/m^2. Laboratory investigations were compatible with ACTH dependent hypercortisolism. Sella MRI showed pituitary adenoma 12 mm in diameter in left side. She was diagnosed as CD, referred to neurosurgery. While waiting for operation, pregnancy (11 weeks) was determined. Her pregnancy had been developed after diagnosis of CD. Urinary free cortisol(UFC) excretion was 992 μg/24 hr (N:36–192 μg/24 hr). In the 2nd trimester, TSS was performed at 18th week of gestation and ACTH secreting pituitary adenoma with Ki67 2% was confirmed. As her postoperative 3rd day serum cortisol was 23 μg/dl, no need for steroid replacement was found. Postoperative UFC on first month was 152 μg/24 hr. At 6th week postoperatively, she was admitted with hypotension and nausea. Basal serum cortisol was 6.34 μg/dl. But enough increment was determined at 250 μg ACTH stimulation test (peak 33 μg/dl). Due to her low basal serum cortisol inspite of pregnancy, symptoms compatible with adrenal failure and only 6 weeks past from TSS, steroid replacement therapy was started for secondary adrenal failure with hydrocortisone 15 mg/day. Her complaints regressed after therapy. At 31st week of gestation, she gave birth to a baby by C/S. There were no complications for mother in peripartum period. The infant was treated for congenital pneumonia and jaundice in neonatal intensive care unit. Steroid replacement was stopped as hypothalamo-pituitary-adrenal axis was found to be normal with 250 μg ACTH stimulation test (peak cortisol: 23.31 μg/dl). On postpartum 2nd month, she was totally fine with BMI 26,17 kg/m^2, basal serum cortisol: 6.63 μg/dl, 1 mg DST: 0.56 μg/dl, UFC: 60.8 μg/24 hr.
Discussion
Pregnancy is rarely encountered during CD. Hypercortisolism is associated with increased maternal and fetal morbidity and mortality. UFC is the preferred test for diagnosis and follow-up during pregnancy. Management of patients should be performed at experienced centers and TSS should be considered as priority.
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P710

A case of diabetes insiputus due to ectopically located neurohypophysis presented during pregnancy

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Background
Gestational diabetes insipidus (DI) is a rare complication of pregnancy, usually developing in the last trimester and resolves spontaneously 4–6 weeks *post-partum.* It is mainly caused by excessive vasopressinase activity, an enzyme expressed by placental trophoblasts which metabolises arginine vasopressin (AVP). However in some cases, it can develop in a patient who had limited reserve of ADH and marginal central DI prior to pregnancy and may not resolve after delivery. Herein we represent a case of DI developed in pregnancy and consisted after delivery due to ectopically located neurohypophysis.
Case
24 year old female patient admitted to our clinics with the complaints of polyuria and polydipsia. The amount of daily consumed water was 18 l. The complaints were started in the last 2 months of pregnancy and did not resolve in 2 years after delivery. She did not have any previously diagnosed psychiatric illness such as obsessive compulsive disorder, somatization or depression. She did not have history of head trauma or symptom or sign of any pituitary hormone deficiency. She was not using any drugs which could be related with DI. In the basal biochemistry, the serum Na level was 143 mmol/l, serum osmolarity was 293 mosm/l. The urine osmolarity was 93 mosm/l. Anterior pituitary hormone levels were normal except mildly elevated prolactin (29 ng/ml). She was hospitalized for water deprivation test. During the test, urine osmolarity did not change with water deprivation but became %200 concentrated after vasopressin which was compatible with cental DI. In the pituitary MRI neurohypophyseal T1-bright spot situated ectopically in the infundibulum. Desmopressin nasal sprey was started and the symptoms resolved immediately.
Conclusion
Gestational DI is a rare complication of pregnancy occurring in two to four out of 100,000 pregnancies. It usually develops at second half of pregnancy and remits spontaneously 4–6 weeks after delivery. Serum and urine osmolality are required for the diagnosis, but other tests such as serum sodium, glucose, urea, creatinine, liver function may be informative. The water deprivation test is normally not recommended during pregnancy because it may lead to significant dehydration, and should be dane in the post partum priod. After delivery pituitary MRI should be performed at some point to exclude lesions in the hypothalamo-pituitary region.
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P711

A case with panhypopituitarism due to aneursymal hemorrhage of internal carotid artery and coil embolisation

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Aneurysmal subarachnoid hemorrhage has been reported to be associated with hypopituitarism. Also, internal carotid artery coil embolisation for aneurysmal hemorrhage is a rare cause of hypopituitarism. 58-year-old female patient who admitted to Emergency Department of Gazi University Medical Faculty due to visual loss and severe headache that did not respond to analgesics accompanied by nausea-vomiting starting 4–5 days ago. Sixth cranial nerve paralysis and bilateral temporal hemianopsia were detected in the neurological examination. In the Cranial computerised tomography (CT), there were widespread subarachnoid hemorrhages. In the Cranial CT Angiography, an aneurysm (29×18×18 mm) involving the cavernous segment of the right internal carotid artery (ICA) was observed. For this reason, selective cerebral angiography was performed. Coiling embolisation was performed for the aneurysm. Later, the complaints of mouth dryness, polyuria, polydipsia, and fatigue were developed in 2–3 days after subrachnoid hemorrhage and coil embolisation. The laboratory analysis showed that Na: 149 (136–145) meq/l, urinary density: 1008 (1010–1020), IGF-1: 78.5 (81–225) ng/ml, GH: 0.36 (0.01–8) ng/ml, ACTH: 19.6 (0–46) pg/ml, Cortisol 1.52 (4.6–22.8) μg/dl, FSH: 5.53 (23.9–119.1) mIU/l, LH: 0.36 (16.3–54.8)

mIU/l, E_2: 11 pg/ml (10–28), prolactin: 0 (2.4–20.9) ng/ml, TSH 0.47 (0.57–5.6) μgIU/ml, free T_3: 1.3 (2.3–4.2) pg/ml and free T_4: 0.9 (0.74–1.52) ng/dl. In the cranial MRI after the procedure, aneurysm lumen was filled with coils and its mass effect caused substantial displacement of the hypophysis gland to the left side. Clinical features, laboratory findings and imaging suggested panhypopituitarism associated with aneurysmal hemorrhage of internal carotid artery as well as procedure of coil embolisation. Corticosteroid, vasopressin and levothyroxine replacement treatment were started. After the hormonal replacement therapy, general condition of the patient and vision improved, nausea and vomiting stopped and urine output decreased. In conlusion, we presented a rare case who had panhypopituitarism including diabetes insipidus developed in 2–3 days after aneurysmal hemorrhage of internal carotid artery and coil embolisation of carotid artery aneursym. This rare cause of pituitary dysfunction should be kept in mind in the clinical setting.

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P712

Progressive optic glioma and concomitant precocious puberty: case report

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Low-grade gliomas are the most common brain tumor in children, accounting for 30–50% of central nervous system tumors in the pediatric age group. They can occur anywhere within the central nervous system (CNS) including the optic pathway (5%). When optic gliomas involve the hypothalamus, patients will often present endocrinopathy. Signs of such involvement can include growth failure and precocious puberty. In this report, we present the case of 8 years three months girls with the history of Low-grade glioma of the Optic pathway diagnosed at the age of 1 year 8/12 in the context of visual acuity loss, nystagmus, and optic nerve pallor on examination. She underwent chemotherapy with periodic control by the carcinologiste. In the follow up since the age of 7 years she developed a progression of her glioma with concomitant linear growth acceleration. At the age of 8 years, she was referred to our department for breast development. On physical examination, his weight was 54 Kg (60–75p) and height was 141 cm (+3DS). Breast development were compatible with tanner stage 3 and no pubic hair was present. Ultrasound imaging showed ovaries were prominent (right ovary: 2× 1 cm and left ovary: 1,8×1 cm) with absence of follicles, uterus was measuring about 4×2,5 cm Biochemical measurements revealed a basal (FSH) level of 6.28 mUI/ml, LH level of 2.63 mU/ml, and Estradiol level of 58.39 ng/l. The bone age was 15 years. The patient was diagnosed with central precocious puberty and started on gonadotropin-releasing hormone (GnRH) agonist treatment (triptorelin acetate 11.5 mg every 3 months). During follow up, 6 months of starting treatment, his progression of puberty has been arrested. With this case report, we would like to emphasize that the growth acceleration in a young child presenting a glioma of the optic pathway should alert the physician to consider a diagnosis of precocious puberty at the early stage.

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P713

A singular case of hypohidrotic ectodermal dysplasia associated with acromegaly

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Hypohidrotic ectodermal dysplasia (HED) is a rare genetic disorder characterized by the faulty development of the ectodermal structure, resulting in most notably anhydrosis/hypohydrosis, hypotrichosis and hypodontia. Affected individuals tend to have sparse scalp and body hair (Hypohidrotic), absent teeth (hypodontia) or small and pointed teeth. HED is associated with distinctive facial features including a proeminent forehead, thick lips, and flattened bridge of the nose. These facial features can also be noted in acromegalic patients who developed gradually changes including enlargement of the forehead, and nose; and thickened lips. Here we describe a singular association of these two pathologies. A 27 year men with no prior medical history, presented with diabetic ketoacidosis. On further complaints, he reported increasing shoe size, intermittent headache. Acromegaly was suspected and was confirmed by elevated GH under hyperglycemia (0.8 ng/ml), and elevated IGF-1. Pituitary MRI was indicated. The intraoral examination revealed partial edentulism with a single tooth erupted in the lower jaw since childhood. Lips were everted. He had sparse, thin, lightly pigmented scalp hair. There was periorbital hyperpigmentation. When asked about a similar history in the family patient gave a positive history of his nieces (brother's daughters) suffering from a similar complaint of edentulism. These findings matched typical features of anhidrotic ectodermal dysplasia. To our knowledge this is the first case of the literature reporting the association of Hypohidrotic ectodermal dysplasia with Acromegaly. These too pathologies can share some facial features. A minitious examination of acromegalic patient can reveal such underlying disease.

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P714

Sever hyponatraemia and SIADH secondary Bartezomib: case report

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Introduction
The Syndrome of Inappropriate Antidiuretic Hormone (SIADH) is considered to be the most common cause of euvolemic hyponatremia. The most common malignancy associated with SIADH is small cell lung cancer with multiple myeloma only observed in few cases worldwide of SIADH. The first line of treatment used in multiple myeloma chemotherapy currently is a proteasome inhibitor, Bortezomib, which is considered significantly more tolerable compared with traditional chemotherapeutic drugs. Bortezomib has been reported to have a wide-ranging side effect profile affecting different systems. However, the endocrine system is rarely affected in patients receiving bortezomib. Eelctrolyte disturbance has been reported in 1–10% of patients treated with Bortezomib with sever hyponatraemia reported in 2.6%. We present a case of Bortezomib induced SIADH with sever hyponatraemia in a newly diagnosed multiple myeloma, with other potential causes of SIADH excluded. A tumour-related cause was deemed very unlikely as hyponatremia was only observed after treatment with Bortezomib and was not present at the time of diagnosis of multiple myeloma.
Case
A 71-year-old lady who was recently diagnosed with IgG kappa multiple myeloma with multiple lytic lesions (skull, cervical spine, thoracic spine) presented to the haematology clinic with progressively worsening fatigue, shortness of breath and dizziness following day 22 of her chemotherapy cycle. She was clinically euovolaemic with no neurological compromise. A blood test showed severe hyponatremia (107 mmol/l) and she was referred to the acute medical unit for admission. A diagnosis of SIADH was made according to Bartter-Schwartz criteria. Her serum osmolality was 226 mOsm/kg [275–295 mosm/kg], urine osmolality was 119 mOsm/Kg [300–900 mOsm/kg] and, her urine Na was 49 mEq/L/day. her Cortisol level and TSH were normal. A chest X ray and CT head were normal. Her sodium level gradually improved in a progressive manner following fluid restriction to 750 ml/day with close monitoring.Her Sodium level on discharge was 135 mmol/L. Bortezomib injection were stopped and her symptoms have improved dramatically.
Conclusion
Health care practitioners should be aware of the possibility of Bortezomib-induced hyponatremia. Close clinical and laboratory monitoring for electrolyte disturbance, neurological disturbances or confusion is essential after initiation of treatment.

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P715

Hypopituitarism due to cerebral abscess

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Introduction
Infectious diseases of the central nervous system (CNS) have been associated with hypopituitarism which relates to the severity, the localization and the cause of the infection. We present here a case of a CNS abscess and hormone deficiencies. A 53 years old man referred to the emergency department of our hospital with high fever and confusion and a 3 day history of weakness and

anorexia. On clinical examination he was febrile (38.4°C), disoriented in time and place, and slightly lethargic. He had ophthalmoplegia, eyelid ptosis, mydriasis and non reactive pupil of the right eye and no other significant findings. Investigations revealed increased white blood cells count, C- Reactive Protein and Erythrocyte Sedimentation Rate. A brain MRI showed a lesion in the sphenoid and cavernous sinus, expanding to the sellar and hypersellar region and retrobulbar oedema in the right eye and he was commenced on intravenous antibiotics. A laboratory evaluation of his pituitary function was performed, which reveal hypopituitarism (Cortisol = 1,8 μ g/dl, ACTH = 4 pg/ml, FSH = 2.41 mIU/ml, LH = 0.29 mIU/ml, Testo = 0.389 ng/ml, TSH = 0.08 μIU/ml, FT4 = 0.83 ng/dl, IGF-1 = 56 ng/ml (71–284 for his age)) and the patient was put on hormonal replacement therapy with hydrocortisone, thyroxin and testosterone. A transphenoidal approach to the lesion at the sphenoid sinus was performed a few days later and the diagnosis of the cerebral abscess was made, but no pathogens were found, probably because he was already receiving antibiotics. On the 9th day on antibiotics he was apyrexial, alert with no confusion. Six months later he was still on oral antibiotics, clinically well, with great improvement of his MRI brain findings, but he was still requiring hormone replacement.

Conclusions

Hypopituitarism due to cerebral abscess is rare, can occur at an early or a late stage and can be either transient or permanent. Its diagnosis may be difficult, demands great suspicion and these patients need a long term follow up.

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P716

Low-symptomatic PRL-secreting pituitary adenoma in patient with morbid obesity

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Introduction

Obesity is one of the most common endocrine disorders. Obesity can either be a symptom of numerous diseases or be associated with them, including cases, when patient does not have other complaints besides excess weight. This should be considered before initiating obesity treatment.

Case

A 42-year-old male visited endocrinologist, complaining of overweight. Minimum weight from his adulthood was 70 kg, maximum was for that moment–124.5 kg, BMI – 43.3 kg/m^2, waist circumference – 134 cm. Weight increase was gradual, for several years. Patient used to have 3 main meals, physical activity was low. He did not complain of sexual dysfunction, as he was divorced and did not live a sexual life. He did not take any medications. Headaches were infrequent: one time in six months; there was no vision impairment, no clinical features of acromegaly, no galactorrhea, however, patient's habitus was slightly effeminate. Fasting plasma glucose level was 5.3 mmol/l, after 120 minutes OGTT – 8.53 mmol/l, HbA1c – 6.1%, insulin – 24.02, LDL-cholesterol – 3.27 mmol/l. Other parameters of biochemical blood test were within reference range. Endogenous hypercortisolism and hypothyroidism were excluded. Patient's testosterone level was 1.88 nmol/l, LH – 0.24, FSH – 1.77, PRL – 7509 mIU/l. We performed pituitary MRI, which revealed a macroadenoma 18 × 16 × 16 mm in size, with MR-signs of subacute hemorrhage. Patient reported that he had no injuries for the whole year and the last episode of headaches was in several months ago. Perimetry revealed no vision field impairment. We started treating patient with cabergoline and advised him to adhere to a hypocaloric diet with low content of animal fats and quickly digestible carbohydrates, and everyday walking. After 3 months of treatment level of PRL was 502 mIU/l, weight decreased on 19.5 kg (from 124.5 to 105 kg), BMI estimated 35.5kg/m^2. There were some improvements in lab parameters: glucose after 120 minutes OGTT – 7.8 mmol/l, HbA1c – 5.8%, insulin – 16.2, LDL-cholesterol – 3.0 mmol/l. These results were achieved without any pharmacotherapy of obesity. Patient continued therapy with cabergoline and follow diet and physical activity guidelines. Repeated MRI is planned after 3 months of treatment.

Conclusion

Our case shows that despite prevalence of primary obesity, associate endocrinopathies should also be taken into consideration. In our patient, a treatment of hyperprolactinemia with cabergoline was accompanied by a decrease in body weight and metabolic parameters improvement, even without pharmacotherapy of obesity.

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P717

Cushing's disease, bilateral adrenal hyperplasia and ARMC5 mutation – case report

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Germline ARMC5 mutations have been described as the most frequent genetic abnormality found in patients diagnosed with primary bilateral macronodular adrenal hyperplasia (PBMAH). PBMAH is a rare etiology of Cushing's syndrome. This gene has been proposed to acts as a tumor-suppressor gene. A 36-years old female presented to us with clinical signs of hypercortisolism. ACTH dependent Cushing's syndrome was confirmed soon after. Pituitary magnetic resonance imaging (MRI) revealed hypointensed lesion, 12mm in size, in right part of the pituitary gland. At the same time abdominal MRI described bilateral adrenal hyperplasia. Transsphenoidal pituitary surgery was performed and ACTH secreting pituitary adenoma with Crooke's hyaline was found on patohystology. Genetic screening for MEN1 and AIP were negative, but germline mutation was identified in exon 2 (I170V) of ARMC5 gene. LOH in tumor tissue is in course. We continuated 3 months follow up and patient was disease free. Six moths after surgery patient had positive hormonal and MRI findings for pituitary adenoma remnant. Abdominal MRI was still unchainged. In further course patient was treated with stereotactic radiosurgery. On her regular follow up pituitary MRI still shows tumor remnant (6 mm) and adrenal hyperplasia is same in diameter. Functional testing demonstrate lack of cortisol supresion in overnight dexamethasone suppression test and high normal levels of ACTH. We presented a patient with Cushing's disease, bilateral adrenal hyperplasia and ARMC5 mutation. After the treatment, our patient still has endogenous hypercortisolism and inadequate ACTH secretion which is probably due to Cushing's disease. It is also possible that adrenal hyperplasia contribute to hypercortisolemia due to ARMC5 mutation. So far we know that ARMC5 mutation lead to PBMAH. Recent studies have shown that the various ARMC5 isoforms were present in most endocrine tissues including the pituitary, adrenal glands and the pancreas. Future studies are necessary and could possibly indicate if ARMC5 mutation is responsible for multi-glandular tumor syndrome.

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P718

Post-traumatic hypopituitarism – a case report

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Background

Head trauma of sufficient severity, particularly causing fracture to the skull base, can cause deficient secretion of anterior pituitary hormones and vasopressin. Severe hypopituitarism and diabetes insipidus (DI) are common post-traumatic events but they can recover 3 and 12 months afterwards.

Objective

To report a case of a woman with post-traumatic hypopituitarism and DI after car accident.

Case report

A 31 year old woman, was victim of a car accident three months ago, with fracture of the base of the skull following which she was admitted in ICU. A cerebrospinal fluid rhinorrhea remitted spontaneously, and the patients presented with a transient episode of polyuria. After recovery she was discharged without any pituitary substitution therapy. At admission in our Endocrine Dpt. after 3 months, she had progressive fatigue, faintness, diarrhoea, secondary amenorrhea. Pituitary MRI showed a focal anterior pituitary lesion compatible with a subacute hematoma. Clinic and laboratory examination revealed hypopituitarism: central hypothyroidism (TSH = 0.0197 uUI/ml, FT4 = 10.05 pmol/l), low IGF-1 = 21.22 ng/ml, hypocortisolism (ACTH = 1pg/ml, cortisol in the morning (8AM) = 3.84ug/dl); hypogonadotropic hypogonadism, (FSH = 0.86mUI/ml, LH = 0.23mUI/ml, Estradiol = 10pg/ml), normal prolactin, (6.14 ng/ml), hyponatremia, hypokalemia, anemia (Hb = 10,7g/dl) and inflammatory syndrome (VSH = 39.4mm/h). After starting the correction of cortisol deficiency the subclinical central diabetes insipidus was gradually exposed, leading to polyuria (6.5 l urine/day, spontaneous urine osmolality = 81 mOsm/kg, plasma osmolality = 293 mOsm/kg). In addition to hydrocortisone we started DDAVP and LT4 with net improvement of the clinical condition.

Conclusion
Posttraumatic diabetes insipidus is devoid of clinical signs in the absence of adequate adrenocortical function. Progressive substitution leads to clinical expression of DI. We recommend that patients with major head injury, especially those with fractures of the base of the skull, should be closely monitored for symptoms and signs of endocrine dysfunction. Regular follow-up is then recommended to monitor for possible remission of the pituitary deficits.

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P719

From adrenal incidentalomas to Cushing's disease

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Introduction
Adrenal incidentalomas are asymptomatic adrenal masses found accidentally during routine examination, not intended for adrenal pathology evaluation. The functionality of these lesions must be further investigated. Rarely, bilateral adrenal nodular hyperplasia can be detected in a patient with Cushing's disease. The authors present the case of a patient with possible autonomous cortisol secretion of adrenal origin that eventually emerged as Cushing's disease.
Clinical case
A 69 years old male, with known history of arterial hypertension, dyslipidaemia and ischemic heart disease, was observed in an Endocrinology outpatient clinic due to adrenal incidentalomas in 2015. Upon investigating axillary adenopathies, thoracoabdominal CT scan revealed adrenal nodules measuring 23 and 15 mm on the right adrenal gland and two 16mm nodules on the left gland. All the nodules had typical adenoma features, except one on the left, which was hyperdense but had a homogeneous contrast distribution. The patient had no clinical features of Cushing's syndrome. The patient was evaluated for hormone excess: 1mg overnight dexamethasone test not suppressed (3.8 µg/dl) with an overlapping Liddle test; normal urinary 24-hour cortisoluria: 15.0 µg/24h (4.3–176.0) and ACTH <5.0 pg/ml. Urinary normetanephrine and plasmatic catecholamine levels were elevated, but less than twice the normal value. IMIBG scintigraphy was negative. Aldosterone/active renin ratio was normal; thyroid function and fosfocalcic metabolism were also normal. The authors concluded that the patient had a possible autonomous cortisol secretion and opted for a strategy of surveillance – clinical, analytical and imagiological. Two years later, in 2017, the patient presented with syncope and altered mental status and underwent a cerebral CT scan, showing a large expansive lesion on the sphenoidal body, with enlargement of the sella turcica; a second tumoral lesion on the anterior skull base was described, with cystic and solid areas (possibly a pituitary adenoma). There was no hormonal deficit. Cerebral MRI further characterized the lesion on the sphenoidal body extending to the anterior skull base, possibly a meningioma, craniopharyngioma or a pituitary macroadenoma. The patient was admitted for transcranial surgery. Anatomopathological analysis confirmed the diagnosis of a pituitary adenoma, with positive ACTH immunohistochemistry.
Conclusions
In face of a patient with an ACTH producing pituitary adenoma with bilateral adrenal nodules and an investigation directing towards a possible ACTH-independent hypercortisolism, the possibility of a previous bilateral adrenal hyperplasia, which was posteriorly autonomized, is considered. However, it is not possible to exclude concomitant functional adrenal and pituitary nodules.

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P720

Somatostatin analogue use to treat visual field loss in acromegaly newly diagnosed in pregnancy

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Acromegaly is a rare disease characterised by excessive Growth Hormone production. Subfertility is common in acromegaly and has various aetiologies, therefore pregnancy in acromegaly is rare. The limited data that is available would suggest that pregnancy in acromegaly is generally safe. However, there have been reports of tumour expansion during pregnancy. Here we present a case of first presentation of acromegaly in pregnancy and subsequent rescue of visual field loss with somatostatin analogue therapy. A 32 year old woman presented at 11 week's gestation of a planned pregnancy to her local hospital with headaches. She had a past medical history of asthma and depression. A CT brain demonstrated a pituitary lesion. She was referred to her regional endocrine centre and was noted to have features of acromegaly. She had an oral glucose tolerance test at 12/40 to confirm the diagnosis; her plasma glucose concentrations were in the normal range, however she failed to suppress her plasma GH. Her IGf-1 was also significantly elevated at 82 nmol/L (normal range 9–33 nmol/L). MRI confirmed a $3.2\times2.7\times2.8$ cm mass with significant compression of the infundibulum and optic chiasm. She had a left upper quadrantanopia visual field loss on formal testing. On discussion of both surgical and medical options our patient opted for medical therapy and was initiated on 100 micrograms tds Octreotide subcutaneously at 16/40. Visual fields completely recovered on repeat visual field testing after 2 weeks. At 24/40 there was further deterioration in visual fields, at which point we increased the Octreotide dose to 150 micrograms tds. This once again allowed return of visual fields to normal within 2 weeks. She was diagnosed with gestational diabetes when screened at 14/40. She was initially treated with diet modifications but was commenced on insulin at 22/40 due to elevated fasting capillary glucose readings. There was no significant increase in insulin requirements following the increase in octreotide dose. She remained normotensive throughout pregnancy. Foetal growth continued along the 50th centile throughout pregnancy. An elective caesarean section was planned at 34/40. The foetal weight was 3.2 kg at birth with an APGAR score of 9. She is menstruating regularly post-partum. She is currently stable on 40 mg octreotide LAR and has been referred for surgical intervention. This is the first case we are aware of where octreotide was used to treat visual field deficit in the setting of Acromegaly newly diagnosed in pregnancy.

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P721

Late onset adrenocorticotrope deficiency in combined pituitary hormone deficiency caused by a mutation of the PROP1 gene

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Introduction
PROP1-related combined pituitary hormone deficiency (CPHD) is associated with deficiencies of growth hormone (GH); thyroid-stimulating hormone (TSH); gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH); prolactin (PRL); and occasionally adrenocorticotropic hormone (ACTH).
Clinical case
We report a clinical case of a progressive CPHD in a man presenting with first symptoms of hypocortisolism at the age of 75 years. This patient's initial symptoms were growth retardation, with final height 134 cm. There was a family history of growth retardation, namely his sister. Hypogonadism was present, with incomplete secondary sexual development and associated infertility. Hypothyroidism was diagnosed at the age of 68 years and replacement with levothyroxine was started. At the age of 75, he was admitted in the emergency room with psychiatric symptoms such as confusion and disorientation and hyponatremia. Hypocortisolism was diagnosed, treatment with hydrocortisone was started and it was referred to an endocrinology consultation. At this point cortisol, ACTH, TSH, fT3, fT4, GH, LH, FSH and PRL were measured in basal conditions, confirming central hypothyroidism, hypogonadism and hypocortisolism, a low PRL and GH deficiency. Magnetic resonance imaging evidenced a markedly atrophic anterior pituitary. Molecular analysis of PROP1 gene was performed by PCR amplification and 2 variants were detected ($c.296G>A$ and $c.358C>T$) in heterozygosity in PROP1 gene.
Conclusion
With this clinical case we want to point out the late diagnosis of this patient, despite a complete clinical picture being present. This case also suggests that, in these patients, corticotrophs may be involved at a rather late age.

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P722

Sever protracted hypernatraemia following Hyperosmolar hyperglycaemic state: Case report

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Introduction
Nephrogenic diabetes insipidus is caused by a deficiency in the action of anti-diuretic hormone, and can be life threatening if not treated appropriately. Lithium

is a commonly used mood stabiliser in psychiatry and is known to cause NDI in around 12% of patients. It has been reported in the literature that severe hyperglycemic state may trigger symptomatic lithium-induced NDI in patients who had been on prolonged lithium therapy.

Case

We report the case of a 57-year-old male with a background of bipolar disorder (on lithium for almost 30 years) and type 2 diabetes on OHAs, who presented to A&E following collapse at home. blood test: sodium 148 mmol/L (133–146), blood glucose level of 44 mmol/L (3–6), K 5.1 mmol/L (3.5–5.3), Urea 41.2 mmol/L (2.5–7.8), Creatinine 444 micromol/L (60–110). He was treated for HHS with adequate fluid resuscitation with 0.9% normal saline and intravenous insulin. His sodium level, however, continued to rise reaching 177 mmol/L in 3 days. His urine output ranged from 4 to 9.0 L/day, serum osmolality 366 mosmol/Kg, urine osmolality 206 mmol/L, urine sodium 87 mmol/L, suggesting DI. He received a trial of desmopressin. This failed to reduce his urine output (day 5: 4522 ml, day 6: 4685 ml). Pituitary function test showed hypogonadtrophic hypogonadism, LH 2.3 iu/L (2–9), FSH 0.9 iu/L (2–12), Testosterone 1.2 nmol/L (9–29), normal Thyroid and HPA axis.An MRI pituitary showed no abnormalities. The lack of response to Desmopressin with the normal pituitary morphology and function apart from secondary hypogonadism (which is likely to be functional due to systemic illness) lead us to believe that this is the case of NDI. His lithium level at presentation was 1.04 mmol/L (0.5–1.2). However, lithium serum levels and clinical findings do not always overlap. The clinical situation was complicated by the initial presentation of HHS and AKI, which are normally managed with large volumes of fluids. Through accurate titration of fluids to sodium levels and careful monitoring of hydration status, the sodium level normalised in a gradual progressive manner from 174 to 144 mmol/L over two weeks. Proper glycemic control was achieved with the addition of regular insulin and his acute kidney injury resolved.

Conclusion

Hyperglycemic state with large losses of body water may aggravate and unmask lithium-induced nephrogenic diabetes insipidus (NDI) which had been asymptomatic previously. This case highlights the importance of strict fluid and electrolyte balance in the management of NDI.

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P723

Unusual complication of a pituitary adenoma: Pituitary abscess

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Introduction

Pituitary abscesses are rare entities that can occur either as primary infections or secondarily to different causes. Primary pituitary abscess arises within a previously healthy gland, while secondary abscess occurs in pituitary gland that harbors a pre-existing lesion (adenoma, craniopharyngioma, or Rathke's cleft cyst). Only 23 cases of secondarily infected adenomas were reported in the literature.

Case report

A 38-years-old man presented with an acute worsening of headaches, double vision and mild left ptosis. His medical history was notable for a known and untreated pituitary adenoma. He denied any fevers, chills, night sweats, neck pain, nuchal rigidity, or photophobia. On examination, he was alert and fully oriented. Vital signs were normal without evidence of fever. His neurologic examination was notable for left ptosis and a dysconjugate gaze with mild impairment of the left medial, superior, and inferior rectus muscles. Visual field assessment was normal. The remaining cranial nerve and neurologic examination were normal. After 3 days of hospitalization, the patient developed fever with no meningitis symptoms. C-reactive protein was increased from 20 mg/l to 305 mg/l with hyperleucocytosis at 21000/ml. Magnetic resonance imaging showed a 4.5 cm partially cystic, partially solid contrast-enhancing sellar mass with extension into the suprasellar cistern, the cavernous sinus and to the left internal carotid. Laboratory analysis revealed no hematologic or electrolyte abnormalities. Endocrine studies were notable for central hypothyroidism with low levels of prolactin, adrenocorticotropic hormone, luteinizing hormone, follicle-stimulating hormone and testosterone. Growth hormone and insulinlike growth factor 1 were not measured. An endoscopic endonasal transphenoidal approach to the sella was used to treat this lesion. Clear fluid and thicker purulent discharge were released on opening the cyst wall. The patient was started on broadspectrum intravenous antibiotics, including vancomycin, ceftriaxone, and metronidazole at meningitic doses. Histopathologic Analysis showed pituitary adenoma and robust inflammatory infiltrate composed of predominantly neutrophils admixed within the neoplastic cells. Tumor cells were positive for human growth hormone, prolactin, adrenocorticotropic hormone.

Conclusion

Pituitary abscesses are rare disorders responsible for high mortality risk. Mortality and morbidity can be reduced by early surgical drainage and appropriate antibiotic treatments. The typical MRI findings are of high importance for the diagnosis of the disorder. The transsphenoidal approach should be preferred in surgery and appropriate antimicrobial therapy should be administered according to the surgical specimen's culture. Additionally, these cases should closely be followed up in terms of pituitary insufficiency, surgical complications and infection.

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P724

Two year old follow up of Hypophysitis secondary to the checkpoint inhibitor Pembrolizumab - a case report

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Ipilimumab (an anti-CTLA-4 antibody) treatment has been associated with Immune Related Adverse Events (iRAEs) of the endocrine system. However the frequency of iRAEs in programmed cell death (PD-1) receptor agent use is incompletely characterised, though initial studies report an incidence of 0.5%. We present a case of Pembrolizumab-induced hypophysitis in a 47 yo. male with melanoma. Presenting in 2007 with an initial diagnosis of melanoma, with lymph node recurrence in 2013. He entered adjuvant clinical trial of Vemurafenib versus placebo (patient unblined to placebo arm). In 2015 he presented with oligometastatic M1a disease and received 4 courses of Ipilimumab. During this Ipilimumab treatment he had a sarcoidosis-type reaction and erythema nodosum. Pembrolizumab therapy was introduced due to progression of melanoma. While asymptomatic his TSH fell from 0.988 pre-treatment to 0.1 mIU/ml after third course of therapy with fT4 13.43 pmol/l pre vs 15.33 pmol/l post. MRI pituitary was normal. Synacthen test (post stimulation cortisol 570 nmol/l) was normal with a normal GCT for cortisol + Growth hormone. Thyroid USS and uptake scan were normal, TPO and TRAb negative. TSH recovered over 5 days reaching 2.92 mIU/ml. A diagnosis of Grade 2 hypophysitis was made and patient was discharged well. He re-presented 10 days later with severe headache and TSH was 0.045. He received pulse iv steroids then oral steroids as per protocol for Grade 3 hypophysitis. While he demonstrated deficiencies in thyroid and sex hormones requiring temporary supplementation he ultimately had a full recovery in regard to his pituitary function and steroids were tapered to discontinue in full. At 28 months Cortisol was 247 nmol/l (1 pm), TSH 0.557 mIU/l, FT4 13.8 pmol/l, Testosterone 18.8 nmol/l, FSH 2.41, LH 2.03, Prolactin 127 mIU/l. He subsequently commenced immunotherapy with Vemurafenib and Cobimetanib developing transient inflammatory like arthritis which responded to anti-inflammatory therapy and dose reduction in Venurafenib. While hypothyroidism is noted commonly in patients receiving Pembrolizumab, hypophysitis is rare. The recognition and management of hypopituitarism and particularly potential associated adrenal insufficiency is increasingly important in the endocrine management of oncology patients. Our case exemplifies that hormone replacement may not be required longterm in such patients. This case demonstrates the potential to be hormone replacement free post pembrolizumab indused hypophysititis at long term follow up. As these agents are used increasingly in the future this case report may help to direct endocrine management of iRAEs.

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P725

Meningoencefalitis as a complication of transsphenoidal surgery of a pituitary adenoma: case report

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Introduction
Transsphenoidal surgery is the preferred approach in patients with pituitary tumours. Transsphenoidal resection of pituitary tumors may account for as much as 20% of all intracranial operations performed for primary brain tumors. Meningitis is a rare complication accounting for less than 2% of procedures.
Methods
We report the case of an elderly patient with a sellar mass who was admitted to the hospital with a central nerve system infection 15 days after brain surgery (transsphenoidal resection).
Results
We present the case of a 77 years old woman with no personal history of interest except for primary hypothyroidism in treatment with 50 mcg of L-thyroxine, who was diagnosed of a sellar mass of 4.5 cm as she was being studied for headache and severe visual loss. This lesion was compatible with a macroadenoma with suprasellar extension with mass effect on optic chiasm. No campimetry could be performed due to severe visual impairment. Hormonal evaluation showed mild-moderate elevation of prolactin (86.9 ng/ml; Normal range 10-30), probably related to pituitary stalk compression, moderate elevation of gonadotropins considering her postmenopausal state (LH 9 μU/ml; FSH 24 9 μU/ml), undetectable levels of IGF-1 and normal levels of cortisol and thyroid hormones. With the diagnosis of pituitary macroadenoma of 4.5 cm with optic chiasm compression and 2 pituitary axis affected (somatotropic and gonadotropic axis) she underwent transsphenoidal resection of the tumour. Inmediately after surgery cortisol and free thyroid hormones levels decreased and she was discharge of hospital with hydrocortisone 30 mg per day and L-Thyroxine 88 mcg per day. 15 days after surgery our patient was admitted to the hospital with headache, confusion and disorientation. No other neurological focal signs were found. A lumbar puncture showed 5440 leukocytes/μL (98% polymorponuclear); glucose 1 mg/dl and proteins 180 mg/dl indicating a bacterial infection, however, no microbiological findings were seen on CSF cultures. After 15 days of treatment with Meropenem, Vancomicyn and Ampicilin our patient recovered completely and was discharged with her usual substitution treatment. She had not presented any other complications so far.
Conclusion
Transsphenoidal surgery is the most common approach for removing pituitary adenomas. Meningitis is a rare complication of this technique but we must consider it in those patients who present with neurological signs, fever or headache after pituitary surgery.

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P726

A family with Kallmann syndrome due to a novel *FGFR1* mutation

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Introduction
Kallmann syndrome (KS) is a developmental disorder characterised by hypogonadotropic hypogonadism and anosmia. Known genetic causes account for up to 30% of patients with KS, with *FGFR1* mutations being identified in 10%. FGFR1-related KS has an autosomal dominant inheritance with incomplete penetrance. We present a family with KS due to a novel variably penetrant *FGFR1* mutation, where the presenting features included cleft lip/palate and anosmia.
Case presentation
A 9-year-old girl (proband) was referred to the Endocrinology Department with short stature, cleft lip and later anosmia. Her height was 122.9 cm (SDS −1.29; MPH 68th centile) with weight 23.1 kg (SDS −1.3); she was prepubertal. Laboratory tests showed undetectable LH and FSH, with normal concentrations of other pituitary hormones. MRI showed structurally normal pituitary gland and olfactory bulbs. Her 6-year-old brother presented with previously repaired cleft lip and palate, short stature and later anosmia. His height was 110.5 cm (SDS −1.18) with weight 18.2 kg (SDS −1.36). He had normal prepubertal genitalia, with testicular volumes of 2 ml. Basal pituitary function was normal. MRI revealed a small anterior pituitary. Molecular analysis revealed a heterozygous deletion, c.915delG, in exon 8 of *FGFR1* in both siblings, resulting in a truncated protein, p.[Glu305AspfsTer17], that is not present on the ExAC Browser. It was inherited from their father who had normal height (SDS 1.23) and fertility, although his puberty was late. The proband was still prepubertal at age 11.5 years, with poor growth. Additional investigations included a glucagon stimulation test with normal response (peak GH 29.3 mcg/l) and GnRH stimulation test with LH and FSH peaks of 1.4 U/l and 1.3 U/l, respectively. Oestradiol was undetectable. She started treatment with ethinyloestradiol, with subsequent pubertal development and improved growth. She also had an audiogram that revealed mild conductive hearing loss. Her brother is currently 11 years old and is growing normally (height velocity 4.9 cm/yr). A GnRH test will be performed at the appropriate age.
Discussion
This case reflects the clinical heterogeneity of KS due to *FGFR1* mutations. In KS, other developmental anomalies can occur, including renal agenesis, skeletal anomalies, hearing impairment, and cleft lip/palate, the latter occurring in 25–30% of patients with FGFR1-related KS. Here, both siblings presented with cleft lip or palate, and the proband had conductive hearing loss. Interestingly, they also both developed *café au lait* spots; whether this is an unreported feature of *FGFR1* mutations is uncertain.

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P727

Cushing disease and pregnancy: Report of 2 cases

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Introduction
Cushing's syndrome usually causes hypogonadism. Occurrence of pregnancy in this context is rare, and is associated with significant morbidity and perinatal mortality. We report two cases of pregnancies in two patients with Cushing's disease.
Case 1
Our first Patient was 37-year-old who presented during the second trimester of pregnancy a Cushing syndrome. The positive diagnosis was made regadless clinical signs and a hight free urinary cortisol at 4839 nmol / L, ACTH was normal at 4.4 pmol. The retaining etiology was a macroadenoma mesured 17×11× 10 mm lowering the sellar floor and opto-chiasmatic tanks with visual field impairment: presence of central scotomas and devices. Treatment consisted of a transsphenoidal resection at 13 weeks of prangnancy. Evolution was marked by the occurrence of spontaneous abortion 16 days postoperatively.
Case 2
Our second patient was 35-year-old and operated for Cushing's disease with recurrence of her illness. The indication of revision surgery for a microadenoma was made after medical preparation by ketoconazole which was interrompted at the discovery of a 6 weeks pregnancy. In the absence of clinical and biological signs of disease activity revision surgery was scheduled after childbirth. Pregnancy was achived without maternal or fetal complications.
Discussion
Cushing's disease and pregnancy is a rare combination and it can causes a therapeutic management problem with a high risk of maternal and fetal complications.

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Developmental Endocrinology

P728

CNNHC: Preliminary results of treatment with recombinant somatropin

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Introduction
Treatment with recombinant Somatropin (rSMT) is safe and has greatly improved the approach of children and adolescents with somatropin deficiency (SMTD) and other growth disorders. In our country, rSMT therapy is approved for isolated/multiple somatropin deficiency, small for gestational age (SGA), chronic kidney disease (CKD), Turner syndrome (TS) and Prader Willi syndrome (PWS). A National Commitee (CNNHC) is responsible for the analysis of each case and treatment approval.
Methods/design
We performed a restrospective and comparative study of 111 patients who completed rSMT treatment, monitored by the CNNHC. The parameters evaluated included midparental target height (MTH), sex, diagnosis, duration of treatment and age, height, growth velocity (VC) at the beginning and end of treatment. Children with isolated SMTD and multiple pituitary deficiency (group 1) were compared to children in need of supraphysiological doses of rSMT (group 2). The association between variables was evaluated using paired samples *t*-test and the independent samples t-test.
Results
Most patients were female (58%) and mean age at the beginning of treatment was 9.8 ± 3.5 years; mean duration of treatment was 6.3 ± 3.4 years. Isolated SMTD was the most common cause (51%), followed by TS (30%), multiple deficiency (7%), CKD (6%), SGA (5%) and PWS (1%). The highest increase of stature was observed in the group of children with isolated SMTD (mean SDS variation of $+1.4$), followed by multiple pituitay deficiency ($+1.38$), CKD ($+1.2$), ST ($+0$, 5), SGA ($+0.47$) and SPW ($+0.29$). When comparing both groups, we found that, prior to treatment, GV is higher in group 2 children (3.6 cm/year vs 4.4 cm/year; $P=0.014$). In group 1, mean baseline height was higher (122.4 ± 19 cm *versus* 113.6 ± 18 cm; $P=0.019$), as was the final height (155.7 ± 12 cm vs 145.8 ± 11.8 cm, $P < 0.001$) and the mean SDS variation (1.43 vs 0.63, $P < 0.001$). The difference between final height and MTH was higher in group 2 (-5.3 cm vs -13.2 cm; $P=0.001$).
Discussion
The primary goal of rSMT in children is acceleration of growth velocity to promote normalization of growth and stature appropriate for the child's genetic potential. This preliminary study suggests that children with isolated/multiple rSMT deficiency show better results with rSMT treatment. However, most patients start treatment quite late and this fact may hinder its efficacy.

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Endocrine Nursing

P729

The value of a holistic needs assessment tool in the care of patients with acromegaly

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Background
It is well established that patients with acromegaly have compromised quality of life both during active disease, as well as whilst on remission. (1). In the recent years, there has been increasing emphasis on the importance of considering health-related quality of life (QoL) outcomes in the care of patients with acromegaly. The University Hospitals Birmingham NHS Foundation Trust introduced and implemented the use of a holistic needs assessment (HNA) tool in the Pituitary Service in 2014.
Aims
To gain a better insight of the needs of patients with acromegaly, as reported by them in the HNA questionnaire.
Patients and methods
A structured HNA, incorporating 11 indicators of psychosocial distress (issues concerning: original diagnosis and treatment; complications; hormone; heart problems; fertility; sexual; psychological; social/family; education/employment; healthy lifestyle, and spirituality/faith/belief) was offered to all patients with acromegaly on arrival at the Pituitary clinic prior to consultation with the health care professional. An audit of the responses was carried out over a 15-month period (May 2014 – August 2015).
Results
A total of 92 patients (with active disease or in remission following various treatments) completed a HNA form. Of the 11 areas assessed, patients were most concerned about their hormone issues (50% of patients indicated that they are either worried/very worried/extremely worried), complications of their condition and treatment (42.39%), original diagnosis and treatment (40.21%), healthy lifestyle (40.21%), and heart problems (36.96%). Additionally, more than quarter (28.26%) of patients expressed concerns about their psychological well-being.
Conclusions
The use of the HNA tool has enabled us to structure and adapt our consultation to focus on what matters most to each individual patient. It is proving to be a very reliable tool in identifying patients' needs as well as identifying the support that patients consider to be a priority.

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Endocrine Tumours and Neoplasia

P730

The down-regulated Tumour suppressor Wnt Inhibitory Factor 1 (WIF1) regulates non-Canonical Wnt signalling in Pituitary Adenomas (PA)

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The Wnt developmental pathway has been implicated in tumour growth and development in a number of tissues. Most frequently, the canonical Wnt pathway acting through the nuclear translocation of B-catenin has been the key player in driving tumour growth. However, non-canonical Wnt pathways, namely the Wnt-Calcium signalling and the Wnt-planar polarity pathways have also been found de-regulated in a number of cancers. In this study, microarray analysis on locally resected PA revealed strong down-regulation Wnt pathway antagonists, namely the Wnt inhibitory factor 1 (WIF1) and the secreted frizzled-related proteins 2 and 4 (SFRP2 and 4). These results have been confirmed by qPCR and shown that WIF1 is under – expressed in all tumour types while SFRP's tend to be repressed in functional PAs. The aim of this study was to functionally assess the role of WIF1 in PA in relation to the different Wnt signalling pathways using two established cell lines, the rat sommatotroph/lactrotroph GH3 and prolactinoma MMQ cell lines in the presence of known canonical and non-canonical Wnt ligands, Wnt3, Wnt4 and Wnt5a. WIF1 over-expression reduced significantly GH3 and MMQ cell proliferation using a fluorescent-based Alamar Blue assay, both in the absence and presence of Wnt ligands. However, both Wnt ligands and lithium chloride, an established canonical Wnt pathway activator, failed to activate β-catenin driven transcription using the TOP/FOP flash luciferase system. In fact, canonical Wnt signalling appears to be completely absent in GH3 and MMQ cells. In order to study the influence of Wnt ligands and their inhibitor, WIF1, on other non-canonical Wnt pathways, the Wnt-Calcium signalling pathway was chosen, owing to the important role that calcium signalling plays in regulating hormone release from these cells. Using the FluoForte Calcium assay (Enzo Biologicals, US) to assess free calcium in real-time in the chosen cell lines, we studied the effect of the Wnt ligands in the absence and presence of the WIF1 inhibitor. Wnt ligands activated calcium release with variable potentials with WIF1 displaying an inhibitory but selective role on this effect. Real-time PCR of targets of the canonical and non-canonical Wnt pathways is also being undertaken together with analysis of growth hormone and prolactin secretion from both cell lines. Preliminary data reveals that the Wnt agonists may activate the Wnt-Calcium signalling pathway and WIF1 could play a role in PA by inhibiting specific aspects of this pathway.

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P731

Cabergoline treatment results in the case of pituitary microadenoma with co-secretion of growth hormone and prolactin

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Introduction
The most frequently secreted hormone in pituitary adenomas is prolactin, but prolactin and growth hormone co-secretion are also seen at not an uncommon frequency. Co-secretion of growth hormone has also been reported after long-term follow up in the prolactinoma patients which well controlled with cabergoline therapy. In this case report, we aimed to discuss the results of cabergoline therapy in a case of co-secreting GH and prolactine with a normal IGF1 level and no acromegalic features at the beginning.
Case
A 58-year-old woman is diagnosed with a pituitary adenoma five years ago. She was being examined for hypoglycemic symptoms but the prolactin level was 82.6 ng/mL(1.2–29.9), pituitary MRI revealed a lesion of 6×5 mm in size and cabergoline treatment was started. After two years, the treatment was discontinued because the patient was asymptomatic, the lesion was shrinking and she was in the postmenopausal period. In the follow-up of third years, patient's showed acromegalic features such as growth in hands and feet, thickening in fingers, in the laboratory examination IGF1 was normal, but growth hormone(GH) was not suppressed with OGTT. Since the size of the mass increased to 9×6 mm in pituitary MRI cabergoline treatment was started again. The pre-treatment IGF1 level was 323 ng/mL(81–225,the patient's age group) at the highest, while the control visits were between 157 and 237 ng/mL. Post-treatment yearly MRIs revealed the mass size decreased to 7×7 mm and stabilized. Cabergoline therapy is planned to be continued due to the absence of significant symptom.
Conclussion
Co-secretion is usually seen in tumors with somatotrophs and mammotrophs together, mammosomatotrophic cell-derived tumors and acidophilic stem cell-derived tumors and usually acromegalic findings were at the beginning in the first two conditions. In the later, acromegaly is added shortly after the presence of the prolactinoma and these tumors are aggressive. Classically, the first treatment option for mixed tumors is surgical. However, cabergoline is effective in both prolactinoma and GH-secreting adenomas. In the present case, it seems that there is a progression in a milder level that can be controlled with cabergoline. Accordingly, it can be argued that some mixed pituitary tumors may be mildly progressive in nature, and in such cases, medical treatment may be an appropriate treatment option for these pituitary tumors with co-secretion of prolactin and GH.

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P732

Pituitary apoplexy after pregnancy in a patient with microprolactinoma

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Case
An 18-years-old female patient suffering from headache, pituitary magnetic resonance imaging (MRI) revealed a lesion compatible with pituitary microadenoma; 8.5×5 mm in size, in the right lateral and extending to the midline of the pituitary gland. Cabergoline treatment was initiated in the external center with a prolactin level of 77 ng/ml and no other pituitary hormone abnormality. Unplanned pregnancy occurred in the patient who continued this treatment for about two months and the treatment was stopped by considering the size of the adenoma. One month later, when the patient is re-evaluated due to increased headache, in the cranial MRI; the size of the pituitary gland was increased and the hypo intense appearance was determined in the posterior part of the gland, which may be significant in terms of bleeding. Then one week after, the patient complained of blurred vision, nausea and dizziness, and applied to the emergency clinic. Repeated cranial MRI in the hospitalized patient was showed bilocular cystic appearance, 12×13×19 mm in size and found to have a fluid-fluid level in the pituitary gland localization, and was compatible with haemorrhage. Patient was had normal visual field and cortisol response and cabergoline treatment started again at the 17th+2 gestational week of the pregnancy and then, headache and other complaints were decreased.
Discussion
Pituitary apoplexy is a rare clinical syndrome characterized by sudden increase in pituitary gland volume due to ischemia and/or necrosis, usually associated with a pituitary adenoma. The coexistence of sudden onset clinical symptoms (headache, visual impairment, ophthalmoplegia) is a defining feature of classical pituitary apoplexy. Most cases are between 50 and 60 years of age and are more common in males and in the non-functioning macroadenomas. Pregnancy is a predisposition due to the formation of a relative ischemic environment by causing hyperplasia in the pituitary. Apoplexy has been reported after cabergoline treatment and it is mostly seen after macroadenomas and follow-up is recommended especially in macroadenomas after treatment. There are only a few reports of microadenoma related apoplexy in the literature. It can be argued that this may be related to the fading of the table and the skipping of the recognition. From this point of view, clinicians should be more careful not to skip the situations where positive results can be obtained with conservative methods like our case.

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P733

Sexually dimorphic gene expression in lactotroph pituitary tumours of different behaviours

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Introduction
Various tumours have a worse prognosis in male than in female. This is also true for lactotroph tumours. Indeed it is known that aggressive and malignant tumours, resistant to dopamine agonists, are more frequent in male than female and are associated to lower ESR1 expression.
Objectives
Our aims are to study the genes differentially expressed and the chromosomic alterations in lactotroph tumours between male and female and their relationships with estrogen pathway.
Material and methods
We compared 30 lactotroph tumours in male ($n=20$) and female ($n=10$). They were classified into 5 grades: benign (grades 1a-1b), invasive (grade 2a), suspected of malignancy (grade 2b) and malignant with metastasis (grade 3). The differential gene expression of all tumours were analyzed with CodeLink Uniset Human Whole Genome bioarrays. The chromosomic alterations using Affymetrix Genome-wide human SNP array 6.0 chip were compared in twelve of them (6 males and 6 females). The differences according to the sex, and the pathological classification was functionaly analysed with Ingenuity pathway analysis (Qiagen).
Results
In these lactotroph tumours, functional analysis of significantly deregulated genes (P value <0.05) showed that cell morphology, cell growth and proliferation, development and cell movement are significantly different between male and female. Among the genes significantly differentially expressed, 120 genes are increased and 20 genes are decreased (fold changes at least 2). Some genes as CTAG2, FGF13 and VEGF-D located on the X chromosome are particularly dysregulated in these tumours. Some of them are involved in the estrogen receptors pathway. CGH analysis highlighted the deletion of the 11 chromosome in 5/6 aggressive and malignant tumours in both sexes, and one chromosomic insertion into aggressive lactotroph tumours only in male. If we compare transcriptomic and CGH analysis, two genes are up regulated in man lactotroph tumours and located on inserted chromosomic region. Both genes are implicated in cell growth and proliferation and may be related to estrogen receptors pathway.
Conclusion
This integrative study demonstrates a sexually dimorphic gene expression and chromosomic alterations in lactotroph pituitary tumours. The differentially expressed genes are implicated in tumour growth, invasion and malignancy and some of them are in relation with the estrogen receptors pathway.

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P734

Comparison of clinical and subclinical apoplexy in pituitary adenomas

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Pituitary apoplexy is a rare syndrome due to a clinically overt hemorrhagic infarction, described in 2–7% of pituitary adenomas. A subclinical usually asymptomatic pituitary hemorrhage and/or infarction may be detected on routine imaging or during histopathological examination in 25–28% of patients with pituitary adenomas.
Aim
We compared the clinical features and evolution of 166 patients with subclinical pituitary apoplexy (SPA) and 46 patients with clinical apoplexy (CA) admitted between 1995 and 2018, diagnosed by suggestive imaging for pituitary haemorrhage and/or pathological exam.
Results
Mean age at diagnostic was 40 years (14–79) for SCA patients and 46 years (16–85) in CA patients, $P<0.05$. Female to male ratio was 2:1 for SCA and 1:1.7 for CA. Macroadenomas were 86% in SCA and 98% in CA patients. In SCA 100 patients (60%) were diagnosed after previous treatments for the pituitary adenoma and 66 patients *per primam* (at the diagnosis of the pituitary tumor), while in CA 91% were diagnosed *per primam*. In SCA about 63% had prolactinomas, while in CA 72% had non-functioning adenomas. Clinically, in SCA 35% had mild-to-moderate headaches (compared to 98% severe headaches in CA), 6% visual field defects (in patients with per primam subclinical apoplexy) versus 80% in CA, none had diabetes insipidus in SCA, compared to 28% in CA patients ($P<0.05$). Hypopituitarism was recorded in 65% of patients with *per primam* SPA and in 42% of those previously treated, as compared to 96% in CA patients, $P<0.01$. Pituitary surgery was done in 17% of SCA patients and 91% of CA patients, radiotherapy in 6% SCA and 13% of CA patients, pharmacological treatment (mainly dopamine agonists) in 76% SCA and 17% CA, no treatment in 19% SCA and 9% CA patients. In patients with SPA, after median follow-up of 71 months, the cure rate was 4.5% in *per primam* SPA and 9% in the second group (none spontaneous). In CA, after median follow-up of 78 months, cure occurred in 25% of patients (spontaneous in 4% of patients). Tumor growth after SPA was recorded in 12–13% of patients and after CA in 2% ($P<0.05$). Conclusion. Subclinical apoplexy in pituitary adenomas is more frequent in males and in prolactinomas, while clinical apoplexy is more frequent in women and in non-functioning adenomas. Subclinical apoplexy does not seem to increase the cure rate in pituitary adenomas.

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P735

Utility of a 3D spheroid cell culture system in neuroendocrine tumors

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In vitro 3D cell culture systems seem to appropriately reproduce the tumor cell microenvironment, including nutrients-oxygen conditions and cell-cell interactions. These models may better mimic *in vivo* tumor conditions and more accurately reproduce drug treatments effects. Since most *in vitro* studies in neuroendocrine tumors (NETs) are performed in 2D culture systems (monolayer), we aimed to compare the monolayer system with a 3D spheroid cell culture system using a human pancreatic neuroendocrine tumor (PNET) model.
Methods
Human BON-1 and QGP-1 PNET cells were used. Total cell number, viability, cell growth, spheroid size, serotonin/chromogranin A (CgA) secretion and somatostatin receptor (sst) and dopamine receptor type 2 (D2R) mRNA expression were assessed in different medium conditions.
Results
Spheroid cultures of BON-1/QGP-1 allowed better cell survival in serum-deprived conditions, compared with monolayer cultures. Total cell number and spheroid size increased in a parallel and time-dependent manner in BON-1 spheroids. In contrast, the increase in total cell number and spheroid size in QGP-1 spheroids were dissociated, probably due to increased cell compactness. In BON-1, Serotonin and CgA release increased in parallel with the increase in spheroid size and total cell number. Hormone release was evaluated in monolayer cultures only after three days because of decreased cell viability after seven days. PNET spheroid growth exhibited time-dependent changes in the mRNA expression of sst subtype and D2R receptors, which was most evident in QGP-1.
Conclusions
These results suggest that spheroids 3D cultures may be a novel method for evaluating cell proliferation and secretion in NET cell models and could help to explain the heterogeneity in NETs. Spheroid cultures grow relatively serum-independent and spheroid size is not an appropriate measure of cell growth in 3D QGP-1 cultures.

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P736

Exposure of GH in acromegalic patients associated with sleep apnea, but not other clinical results: Experience of a center from 2006 to 2017

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Aim
Acromegaly is associated with premature dead and a number of risk factors for cardiovascular disease (CVD). We aimed to examine the concept of cumulative GH exposure with regard to the presence these risk factors and cancer in acromegalic patients.
Methods
Retrospective observational study in all acromegalic patients from 2006 to 2017 with a minimum of 3 years of follow-up. We exclude patients not treated. GH exposure was calculated as median GH or IGF1 multiplied by the years of follow-up. We also calculate IGF1, % IGF1 above ULN for sex and age. We also used Sagit scale to access comorbidities. We review clinical registries of those patients, and categorized them in disease remission, controlled by therapy or active disease. We used descriptive statistics, t-test for continuous variables and chi-squared distribution for categorical variables. The threshold for statistical significance was $P<0.05$ for each test.
Results
We found 77.9% macroadenomas, 18.2% microadenomas and 3.9% invasive in 78 acromegalic patients. The mean age at diagnose was 51 ± 18.9 years and 68% were female. Most patients were submitted to surgery and transphenoidal resection was the first treatment in 76.2% of patients. Radiotherapy was used in 2.6%, in the early years for those who refuse the surgery. As first therapy, somatostatin analogues were prescribed in 6.6% of patients and dopamine agonists in 10.3% reflecting the high frequency of somatomammotrophic pituitary adenomas. They were followed-up for 12.0 ± 0.2 years. The same drugs, Pegvisomant, subsequent surgery or radiotherapy were also used for those that do not achieved the safety levels of the guidelines. At the last evaluation 42.3% of the patients were on remission, 38.5% had the disease controlled by therapy and 19.2% had active disease in spite of the current treatment. The prevalence of hypertension was 65.4%, diabetes 39.4%, coronary artery disease 32.1% and 14.1% had also cancer. Only sleep apnea (present in 10.3% of patients) was significantly associated with the IGF1 exposure ($P=0.043$). Death occurred in 15.4% of patients during the follow-up. They were older with longer duration of follow-up. GH exposure was significantly associated with larger tumors with supra selar extension.
Conclusions
We found significant associations between GH or IGF1 exposures with larger tumors, but not with the prevalence of CVD, CVD risk factors or cancer. Only OSA was significantly associated with IGF1 exposure. These findings are new and deserve further evaluation in larger populations, with a prospective design.

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Female Reproduction

P737

Prolactinomas and Pregnancy: pregnancies medically induced...

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Introduction
Prolactinomas are the most common hormone secreting pituitary adenomas. Also hyperprolactinemia is the cause of a third of all cases of female infertility, yet with

adequate management, most patients are able to achieve pregnancy. The purpose of this paper is to reporte the effectiveness of medical treatment in restoring fertility, while managing prolactinoma.And also to illustrate the follow-up of prolactinoma during pragnancy.
Cases
The first patient was 32 years old, had galactorrhea associated with amenorrhea about 3 years ago. Subsequent investigations revealed hyperprolactinemia. Pituitary MRI confirmed a sellar lesion (<1 cm). the therapeutic decision was to treat with Cabergoline.The second patient was 42 years old, had a macro-prolactinoma revealed by cycle disorders installed 17 years ago, complicated 4 years later of spontaneous galactorrhea. The investigations revealed an hyperprolactinemia with a sellar lesion measuring 11×11 mm, because of financial problems, the patient could not receive medication and got complications such us, visual disturbances and headache, with increasing of the size of the tumor (12 mm×16 mm). She was treated immediately with Cabergoline.The third one was a 41 years old patient, she had a macro-prolactinoma revealed by secondary amenorrhea and galactorrhea with bilateral visual acuity decrease. She was treated with bromocriptine. The three women did not follow the instructions of making contraceptifs précautions and became pregnant after few months of treatment. The management of each case was depending on the tumor volume.
Conclusion
Treatment with dopamine agonists usually restores ovulation and fertility. The treatment with Cabergoline is generally being preferred to bromocriptine because of its higher therapeutic efficacy/adverse effects ratio.

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P738

Sheehan's syndrome: Pregnancy is still possible...

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Introduction
Sheehan's syndrome (SS) is the development of partial or complete hypopituitarism following parturition, preceded in most of the cases by severe postpartum hemorrhage. The disease continues to be common in some developing countries.Some of the anterior pituitary functions like gonadotrophic and corticotrophic secretions may be preserved in these women. The purpose of this observation is to reporte a rare case of spontaneous pregnancy occurs in a patient followed for Sheehan's syndrome, as well as to indicate the principles of management.
Case
H.T. a 38-year-old woman, delivered her first child in 2007 with a delivery bleeding. She didn't had lactation failure and did resume menstrual cycles. She had a cesarean delivery in her second pregnancy in 2010, it was complicated by bleeding as well and was transfused, and was hospitalised 10 days in intensive care. The Investigations revealed central hypothyroidism and cortisol deficiency. She was put on hydrocortisone and Levothyroxin. She had also developped spaniomenorrhea. Five years laters, the patient was prangnant and was reffered to us for the follow-up, whitch was based on clinical and biological monitoring of substitutions associated with obstetrical monitoring. The birth took place without incident. The MRI had objectified an empty sellar.
Discussion
Spontaneous pregnancy rarely occurs while Sheehan's syndrom. Hypopituitarism during pregnancy should be followed strictly, and normal hormone levels should be achieved before any pregnancy. In our case, after the confirmation of Sheehan's syndrome, menstrual cycles remained irregular, the patient was not taking contraception, although she did not want a child. The patient received informations about the safety of her pregnancy if followed- up regularly. Indeed, it has been reported that inadequate hormone replacement in pregnant women with Sheehan's syndrome cause miscarriage in 50% cases and 27% of maternal mortality.
Conclusion
Because of hypopituitarism signs are non specific, the diagnosis of Sheehan syndrome should be considered, in any patient with postpartum hemorrhage history. In patients with preserved gonadal function, contraceptive use should be recommended.

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Growth Hormone IGF Axis - Basic

P739

Craniofacial fibrous dysplasia and long-term untreated GH excess in McCune–Albright syndrome

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Introduction
Craniofacial fibrous dysplasia, characteristic of McCune-Albright syndrome (MAS), is usually present in patients with MAS related GH excess, and complicates their neurosurgical approach. We describe a 21-year-old male with severe craniofacial fibrous dysplasia and acute obstructive hydrocephalus due to a 39×35 mm cystic lesion in the third ventricle that occluded Monro's foramina, in whom MAS and long-term untreated acromegaly were discovered.
Methods
This report describes the presentation, diagnostic process, treatments and outcome of a young male patient with abnormal dysplastic growth of craniofacial bone structures, that reduced the optic canal and orbits, and occupied completely the sphenoid sinus, who presented with rapidly progressive headache. It also includes the results of a detailed GNAS genetic study in blood, pituitary, and bone tissues.
Results
Surgical resection of the tumor using a transcranial transcortical-transventricular approach and opening of the suprasellar cistern resolved the hydrocephalus and associated symptoms. Histologic and genetic studies of the extracted tissues, together with a hormonal evaluation, confirmed the presence of a colloid cyst combined with a GH-secreting pituitary adenoma with a Ki 67 proliferative index of 9%, and MAS. The GNAS gene p.Arg201His mutation in mosaicism was present in the pituitary tissue, but was not found in blood and decalcified paraffin-embedded bone tissue. Adequate control of his GH hypersecretion with somatostatin analogs and cabergoline was achieved.
Conclusion
This is the first reported case of a colloid cyst of the third ventricle in a patient with MAS. Our results suggest that MAS related long-standing GH excess may promote abnormal progressive dysplastic growth of craniofacial bones that might force any entrapped intrasellar lesion to grow upwards to the third ventricle, and should be ruled out and treated promptly in young patients with fibrous dysplasia. Hormonal evaluation and multidisciplinary approach before any surgery in these patients may help to optimize surgical results and guide further treatments to avoid long-term deleterious impact of hyperfunctioning endocrinopathies.

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P740

GH replacement therapy (GHRT) in adult patients with GH deficiency (GHD): a long term follow up

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Introduction
GH deficiency (GHD) leads to altered body composition, lipid metabolism and quality of life, and is also associated to an increased cardiovascular morbidity and mortality. The aim of this study was to evaluate long-term changes after treatment with GH replacement therapy (GHRT).
Methods
We retrospectively reviewed adult patients with GHD in our clinic who were treated with GHRT. We evaluated demographic (etiology, age, dose), anthropometric (body composition, bone mineral density), and analytical data (glucose, lipid, hepatic and renal profile, and IGF1 levels), as well as quality of life (QoLAGHDA), at the time of initiating GHRT and after the last dose.
Results
We evaluated 37 patients (31 males, aged 39.4±14 years at the onset of GHRT). There were nine cases of childhood-onset GHRT, seven due to congenital hypoplasia, and 28 cases with adult-onset, mainly due to surgical intervention

after pituitary macroadenoma (14) and craneopharyngioma (4). Patients were treated during 9.2 (2–15) years. Mean duration of follow-up was 10.8 (1–23) years. GHRT dose increased from 0.20 (0.1–1.0) mg at onset, to 0.30 (0.1–1.2) mg at the last follow-up visit ($P=0.05$), and IGF1 levels increased (88 ± 57.2 to 177.4 ± 50.6 µg/l, $P<0.001$). We observed a decrease in body fat mass (36.6 ± 9.3 to 33.1 ± 8.1%, $P=0.011$) and an increase in BMI (26.9 ± 5.0 to 28.4 ± 5.6, $P=0.014$). No significant changes in body lean mass were found. An increase in Hba1c and HDL-C levels was noted (5.1 ± 0.8 to 5.7 ± 0.8%, $P=0.007$, and 51.45 ± 15.0 to 59.88 ± 21.7 mg/dl, $P=0.003$, respectively), but the decrease in LDL-C or triglyceride levels was not significant. No hepatic or renal side-effects were reported. A non-significant increase in vertebral and femoral neck T-score was noted. Quality of life improved (13.7–6.5 points, $P<0.001$). 4 patients developed diabetes (only 2 already presented it at the time of starting GHRT). GHRT was withdrawn due to lack of efficiency, increase in tumor volume or for re-evaluation in 3, 1 and 3 cases, respectively.

Conclusion

GHRT improved body fat mass, HDL-c and quality of life. The effect on glucose metabolism or bone mineral density may be controversial, and other changes were less relevant. The role of these modifications in the overall improvement of the cardiovascular risk in patients with GHD deserves further investigation.

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P741

IGF1 level and GH dose adjustmentin adults with GH deficiency (AGHD): experience from a Registry in France

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Objective

IGF1 is the most useful serum marker for GH dose titration in adults. The authors focused on the GH dose adjustment with extreme IGF1 values (< −2S.D.; > +2S.D.).

Methods

French observational study of AGHD patients treated with Norditropin®. Prospective follow up until 5 years.

Results (median [Q1; Q3]):

328 AGHD, 39.2 ± 14.3 years old were included. GH median dose was 0.30 mg/d [0.20; 0.40]; IGF1 level was available in 97% of patients and was −0.9 S.D. [−7.2; 3.9]. Each year the GH dose modified in around 28% of patients (1st year in 32.6%, 5th year in 25.4%). At the end of the follow up the median GH dose was 0.40 mg/d [0.30; 0.60]. IGF1 measured annually in 80% of patients. Each year around 80% of patients had IGF1 between −2S.D. and +2S.D. During follow up 242 extreme IGF1 values were observed in 145 (44%) patients. And at N + 1 visit no dose adjustment occurred in 72.2% ($N=52$) of patients with IGF1 > +2SD ($n=61$) for a median dose 0.30 mg/d [0.20; 0.40] vs 49.3% (N = 36) with IGF1 < −2 S.D. (n = 49) for a median dose 0.45 mg/d [0.40; 0.60] (Tables 1 and 2).

Table 1 IGF1 < −2s.d. with GH dose adaptation (73 patients) (dose, median, (mg/d) [Q1; Q3]).

N = patients, n = IGF1 values	V N	V N + 1
Dose increase (N = 29, n = 36)		
Dose	0.40 [0.30; 0.55]	0.60 [0.48; 0.80]
Dose reduction, (N = 3, n = 3)		
Dose	0.60 [0.45; 0.80]	0.40 [0.00; 0.40]

Table 2 IGF1 > +2s.d. with GH dose adaptation (72 patients) (dose, median, (mg/d) [Q1; Q3]).

N = patients, n = IGF1 values	V N	V N + 1
Dose increase (N = 7, n = 7)		
Dose	0.30 [0.20; 0.80]	0.40 [0.30; 1.00]
Dose reduction, (N = 25, n = 27)		
Dose	0.60 [0.20; 0.60]	0.30 [0.10; 0.40]

Conclusion

IGF1 was regularly measured in AGHD patients treated with GH in accordance with the guidelines and was in normal range for the majority. In this observational study, extreme IGF1 values were not systematically accompanied by dose adjustment. It could be explained by low GH dose prescribed and the fact that IGF1 is not the single factor of GH dose adaptation. Not taking in consideration at the visit with extreme IGF1 level the efficacy and tolerability of GH treatment is the limitation of this observation.

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P742

Hirsutism as presenting clinical sign of acromegaly

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Case report

Hirsutism although common in acromegaly (24%) is not considered as the prevalent symptom of the disease. Here we describe a seventy-one year old woman with a 2-year history of hyperandronism and subtle acromegalic features (macroglossia, sleep apnea). Clinical examination showed hirsutism (Ferrimann-Gallwey score 20/34), acanthosis nigricans and mild clitoridomegaly. Blood examination revealed elevated IGF-1: 502 ng/ml (69–200 ng/ml) and standard oral glucose tolerance test (OGTT) showed a diabetic curve and failed to show suppression of GH levels (post glucose GH: 1.8 ng/ml). The diagnosis of acromegaly was made accordingly. Laboratory results also revealed elevated levels of testosterone: 4.0 nmol/l (0.35–2.6) and androstenedione: 3.7 ng/ml (0.3–3.5) and normal levels of DHEAS: 2.69 µmol/l (1.77–10.5). Sella MRI was negative for pituitary adenoma. Further imaging failed to identify any cause for GH excess. Ultrasound of the ovaries did not reveal any morphologic abnormalities. The patient was treated with SST analogs with prompt response. Hormonal follow-up and imaging were normal. This case intends to emphasize that hirsutism may rarely be a prominent feature of acromegaly. The recognition of hyperandrogenism in a subset of acromegalic patients with hirsutism as a cardinal feature would facilitate early detection and diagnosis.

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Neuroendocrinology

P743

Desensitization of the human motilin receptor by motilin and motilides

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The motilin receptor (MLNR) belongs to a family of Class I G protein-coupled receptors, and is an important endogenous regulator of gastrointestinal motor function. Motilin and erythromycin (EM), two chemically distinct full agonists of the motilin receptor, bind to distinct regions of this receptor, while the action of these different chemical classes of agonists likely yields a common activation state of the cytosolic face of this receptor that is responsible for interaction with its G protein. In the current work, we studied the desensitization of the MLNR by motilin and motilides in CHO cell line stably expressing the cloned Halo-tagged MLNR. We also studied receptor internalization following application of motilin and motilides visualized by using Halo-tagged MLNR. Desensitization of the MLNR was induced by prestimulation of CHO cells expressing Halo-tagged MLNR with concentration of over 10^{-8} M of motilin, while was not induced by prestimulation with any concentration of EM or other macrolides. Halo-tagged MLNR was trafficking into the cytosol after motilin and EM stimulation and was recycling to cell surface more slowly with motilin stimulation than with EM stimulation. These data supported that it should be possible to develop motilides with high potency and less desensitizing ability.

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P744

Clinical and radiological characteristics of patients with primary empty sella

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Background
The primary empty sella (PES) is radiologically defined as partial when less than 50% of the sella is filled with cerebrospinal fluid (CSF) and pituitary gland thickness is $\geq$3 mm or total when more than 50% of the sella is filled with CSF and the gland thickness is $\leq$2 mm in diameter.The aim of our study was to evaluate clinical and radiological aspects of PES.
Methods
We retrospectively evaluated clinical features and radiological findings of 36 patients with PES followed in the internal medicine department of the Charles Nicolle's hospital and the endocrinology department of the Military Hospital of Tunis between 1992 and 2016.
Results
Our study included 26 women and 10 men with an average age of 47.64 $\pm$ 15.47 years [9–83]. Of the risk factors of PES, multiparity was detected in 76% of the female patients. Obesity, hypertension, diabetes mellitus and autoimmune hypothyroidism were found in 41.6%, 38.9%, 27.8% and 8.3% of the whole study group,respectively. Only one patient had idiopathic intracranial hypertension. Endocrine signs were the most common presenting symtoms (52.7%). More than half of our patients complained of headache. The diagnosis was confirmed by pituitary magnetic resonance imaging (MRI) in the majority of cases. Sixty one of the patients had partial empty sella and the remaining 39% had total empty sella. Other radiological abnormalities on MRI were associated with PES: an absence of the normal posterior pituitary bright signal in 2 patients consulting for polyuria and an optic chiasm ptosis in a patient with campimetric defect. No significant differences were found among the partial and total empty sella subgroups in terms of risk factors of PES.
Conclusion
PES is a radiological entity that is often asymptomatic and discovered fortuitously but can induce variable neurological, hormonal and ophthalmological disorders. This diagnosis must be evoked in a middle-aged, obese, multiparous and hypertensive woman presenting with a symptomatology suggestive of pituitary deficiency or chronic headache.

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P745

Serum sodium is inversely related to frailty and bone mineral density (BMD) in human immunodeficiency virus (HIV)-infected patients

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Background
HIV-infected patients are predisposed to an increased risk of hyponatremia. In healthy population, low sodium is associated with impaired health status and reduced BMD, but less is known about this association in HIV-infection.
Aim
To investigate the relationship between serum sodium, frailty and BMD in a large cohort of HIV-infected patients.
Methodology
A retrospective, observational, cohort study on adult HIV-infected patients (age $\geq$18 years), attending the Multidisciplinary Metabolic Clinic of Modena, was carried out including all sodium examinations performed at the Modena lab from 2007 to 2017 available in a large database. Laboratory ranges of normality for sodium (136–146 mEq/l) were used to subdivide records in hyponatremic (HypoNa), hypernatremic (HyperNa) and normonatremic (NormoNa) groups. BMD was measured at total body, lumbar spine (L1–L4) and total hip using a Hologic QDR-2000 densitometer (DXA). Frailty was calculated through 38-item multimorbidity frailty index.
Statistical analysis
Parameters were not normally distributed and Kruskal-Wallis test, followed by Dunn's test, was used to compare continuous variables. Correlations were performed using linear regression models.
Results
8101 records (5454 from males and 2647 from females) of serum sodium (mean 139.4 $\pm$ 3.1 mEq/l) evaluated in HIV-infected patients (mean age 49.0 $\pm$ 7.9 years) were considered. 617 (7.6%), HypoNa, 44 (0.5%) HyperNa and 7440 (91.8%) NormoNa were found. Frailty score was inversely related to serum sodium ($r = -0.174$, $R^2 = 0.03$, $P < 0.0001$), even after the exclusion of HyperNa group ($R = -0.191$, $R^2 = 0.036$, $P < 0.0001$). Frailty was significantly higher in HypoNa than NormoNa ($P < 0.001$). Considering results at DXA examination, BMD was normal in 30.3% and reduced in 69.7% (54.8% osteopenia, 14.9% osteoporosis). Total body BMD, but not femoral nor lumbar, directly correlated with serum sodium ($R = 0.049$, $P < 0.001$) and it was significantly lower in HypoNa compared to NormoNa ($P = 0.029$).
Conclusions
This study shows that serum sodium is inversely related to frailty, suggesting its potential role as reliable and cheap marker in the HIV-infection follow-up. Furthermore, we demonstrate a direct correlation between sodium and body BMD in HIV-infected patients, similarly to general population.

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P746

Sox 2 expression in human pituitary adenomas-correlations with pituitary function

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Introduction
Sox2 is a widely expressed marker of progenitor and stem cells in various organs, strongly expressed within Rathke's pouch and the neural ectoderm. It exerts a critical role in the early stages of pituitary development but it is still expressed in the adult gland. Sox2 expression in pituitary adenomas and its possible correlation with clinicopathologic characteristics have not been investigated so far.
Aim
To evaluate the immunohistochemical expression of Sox2 protein in pituitary adenomas.
Subjects and methods
We included in the study 34 pituitary adenoma samples (13 GH-secreting, ten prolactinomas with proven resistance to dopamine agonists and 10 non-functioning adenomas) prelevated at the time of the neurosurgical intervention. Tissue samples were analyzed by immunohistochemistry for pituitary hormones and Sox2 expression by the avidin-biotin-HRPA method.
Results
Sox2 positive expression was detected in 16 patients (47.05% of cases) and did not show an association with tumor volume or extension at diagnosis. GH-secreting tumors were immunopositive for Sox2 in 57.14% of cases, prolactinomas in 60% and non-functioning pituitary adenomas in only 20% of cases (significantly higher percentage of Sox2 positivity among secreting tumors, $P = 0.041$). 58.82% of all patients (20 cases) had pituitary insufficiency at diagnosis. At diagnosis, the percentage of corticotrophin and gonadotrophin deficiency was significantly higher in patients with Sox2 negative tumors compared to those with Sox2 positive tumors ($P = 0.047$ and 0.041, respectively). In cases associated with hypopituitarism, the number of endocrine pituitary axes affected was not significantly different compared to Sox2 positive tumors.
Conclusion
Sox2 positive expression is frequent in pituitary adenomas (especially in secreting tumors) but is not correlated to tumor size or invasiveness. However, intratumoral Sox2 expression is associated with a lower percentage of pituitary insufficiency.

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P747

The probability of recurrence of the Cushing's disease within three years after surgical treatment depends on the ACTH and cortisol levels in early post-surgery period

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Objective
The search for the predictors of the Cushing's disease (CD) recurrence after surgical treatment among the following parameters - gender, age, adenoma size, preoperative levels of ACTH (morning) and cortisol (evening) in the blood, postoperative levels of ACTH (morning) and cortisol (morning) in the blood.
Material and methods
A retro- and prospective monocenter study of treatment outcomes in 181 patients with confirmed diagnosis of Cushing's disease who underwent endoscopic transsphenoidal adenomectomy between 2007 and 2014 was performed. The inclusion criteria were: the absence of previous pathogenetic treatment (neurosurgical, medical and radiation therapy) for this disease and the development of remission of the disease in the early postoperative period in the form of adrenal insufficiency or normalization of the morning ACTH and cortisol secretion. The group consisted of 29 men and 152 women. The duration of follow-up period was three years and more. Within 3 years the remission was preserved in 135 patients (24 men, 111 women), the recurrence of Cushing's disease developed in 46 patients (five men and 41 women). Recurrence probability, relative risks (RR) and 95% confidence intervals were calculated.
Results
No relationship between preoperative data (age, gender, adenoma size, preoperative levels of ACTH and plasma cortisol and serum, free cortisol level in daily urine) and the probability of recurrence of CD was found. However, the probability of CD recurrence was associated with levels of ACTH and cortisol in the early postoperative period. In patients with ACTH level less than 7 pg/ml, three year recurrence appeared to be 8%, 95% CI (3%, 17%), while at the level of $\geq$7 pg/ml recurrence was observed in 37% (28%, 46%) cases, RR 0.23 (0.09; 0.51). In patients with cortisol level below 123 nmol/l the recurrence developed in 17% (11%, 24%) of cases, while in patients with cortisol level $\geq$123 nmol/l, recurrence was equal to 50% (35%, 65%), RR 0.34 (0.21, 0.57).
Conclusion
The development of adrenal insufficiency with the decrease in ACTH level less than 7 pg/ml and cortisol level less than 123 nmol/l in early post-surgery period significantly reduces the probability of the recurrence of CD within three years after surgery.
Key words: Cushing's disease, adrenocorticotropic hormone (ACTH), transsphenoidal adenomectomy, cortisol, recurrence.

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P748

Metabolic status, body composition and bone mineral density in 85 patients with childhood onset growth hormone deficiency (COGHD) in transition period

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Transition from childhood to adulthood is particularly important in patients with COGHD mainly because of the associated metabolic abnormalities, inadequate body composition and decreased bone mineral density (BMD). There is a lack of large monocentric studies related to this issue.
Design
Monocentric, observational, retrospective cross-sectional study.
Patients
We collected 85 COGHD patients (58 males, aged 17–26 years) transferred from pediatric to adult endocrinology department from 2005 to 2017. Median age at transfer was 19.9 $\pm$ 1.5 years.
Methods
We investigated the metabolic status (glycaemia and insulin in OGTT, HOMA-IR, lipids, HbA1c), body composition (% fat, fat mass - FM and lean body mass – LBM) and BMD (BMD g/cm^2, Z score-DXA method) of patients at first evaluation after transfer. Related to the etiology of COGHD, two subgroups of enrolled patients were compared. First subgroup consisted subjects with congenital cause of GHD (CH-COGHD) while second subgroup presented patients with history of hypothalamic/pituitary tumor (TU-COGHD). These subgroups were matched by age, sex and BMI.
Results
CH-COGHD was detected in 64.7% cases, while TU-COGHD, idiopathic and other etiologies were reported in 23.5%, 7.0% and 4.7% of patients respectively. All patients had GH replacement during childhood (duration therapy 5.7 $\pm$ 2.0 yrs). The pause in GH replacement was 2.3 $\pm$ 1.7 before the transfer. Isolated GHD showed 18.8% cases, multiple pituitary hormone deficiency 65.8% while 9.4% of patients recovered GH axis. Combined pituitary hormonal loss was frequently reported in TU-COGHD ($P<0.05$). Radiotherapy was performed in 25% of patients with hypothalamic/pituitary tumors. Peak and AUC of insulin in OGTT, HOMA-IR and triglycerids were significantly higher in TU-COGHD ($P<0.05$). Peak and AUC of glycaemia in OGTT, HbA1c, cholesterol, % fat and FM showed also higher levels in TU-COGHD subgroup, but not significantly ($P>0.05$). In addition, LBM, BMD (g/cm^2) and Z score demonstrated lower values in TU-COGHD subgroup, statistically not significant ($P>0.05$).
Conclusion
Patients with COGHD caused by hypothalamic/pituitary tumors are at an increased risk for the metabolic syndrome in transition period. Also, they have a tendency to decreased lean body mass and BMD compared to patients with congenital COGHD. Young adults with COGHD after achievement a final height should be carefully monitored by adult endocrinologist in terms of their metabolic balance, adequate body composition and bone status.

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P749

Latest safety outcomes from the PATRO adults study of omnitrope® for the treatment of adult patients with growth hormone deficiency

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Introduction
Omnitrope® (Sandoz) is a recombinant human growth hormone (rhGH) and was the first biosimilar medicine approved by the European Medicines Agency. PATRO Adults is an international, longitudinal, non-interventional study of the long-term safety and efficacy of Omnitrope® in adults treated in routine clinical practice. The study provides 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
The study includes adult patients who are receiving treatment with Omnitrope® and have provided informed consent. Patients treated with another rhGH before starting Omnitrope® therapy are also eligible for inclusion. The current interim analysis aims to provide data on the risk of glucose intolerance and diabetes.
Results
As of December 2017, 1236 patients had been enrolled on the study; 1038 (84.0%) had adulthood-onset GHD and 188 (15.2%) had childhood-onset GHD. Overall, 629 (50.9%) patients had been pre-treated with another rhGH. Mean (standard deviation (S.D.)) age was 49.4 (15.3) years, and mean (S.D.) BMI was 29.5 (6.3) kg/m^2. In total 3420 adverse events (AEs) in 801 patients have been reported, with 622 (321 (26.0%) patients) of these regarded as serious. One hundred and fifty AEs in 88 (7.1%) patients were suspected to be related to Omnitrope®; these included general disorders/administration site conditions in 20 patients, nervous system disorders in 25 patients and musculoskeletal/connective tissue disorders in 33 patients. A total of 26 serious AEs (SAEs) in 18 (1.5%) patients were suspected to be related to Omnitrope®, leading to treatment discontinuation in six patients. Treatment-related SAEs included two incidences of diabetes. The first case was diabetes mellitus aggravation in a 45 year old male with adulthood-onset GHD, following 4–6 months of GH therapy; Omnitrope® was permanently discontinued. The second case was worsening of diabetes mellitus in a male aged 72 years with adulthood-onset GHD, following 19 years of GH therapy; Omnitrope® treatment was interrupted. Since the start of the study, 263 patients discontinued treatment, of which 25 (9.5%) were due to AEs related to rhGH treatment.

Conclusions
Based on this interim analysis, Omnitrope® treatment in adults with GHD is well tolerated in a real-life clinical practice setting, irrespective of pre-treatment status. The ongoing PATRO Adults study will provide further data on the diabetogenic potential and overall safety of long-term GH treatment in this population.
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P750

The different response of somatotropic system to genistein and daidzein in the rat hypothalamus
Svetlana Trifunović[1], Branka Šošić-Jurjević[2], Milica Manojlović-Stojanoski[2], Nataša Ristić[2], Nataša Nestorović[2], Branko Filipović[2] & Verica Milošević[2]
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The different response of somatotropic system to genistein and daidzein in the rat hypothalamus: Svetlana Trifunović, Branka Šošić-Jurjević, Milica Manojlović-Stojanoski, Nataša Ristić, Nataša Nestorović, Branko Filipović, Verica Milošević University of Belgrade, Institute for Biological Research 'Siniša Stanković', Department of Cytology, Belgrade, Serbia The different response of somatotropic system to genistein and daidzein in the rat hypothalamus Emerging evidence suggests that consumption of nutrients rich in isoflavones may has a beneficial effect on numerous diseases in animals and humans. On the other hand, given the structural similarity with estrogens, isoflavones: genistein (G) and daidzein (D), may cause adverse health effects via endocrine-mediated mechanisms in an organism. Our prior results has demonstrated that G exposure, could significantly increase activity of somatotropic system in the hypothalamus. Exactly, genistein's treatment increased: the arcuate (Arc) nucleus volume, the volume density of growth hormone releasing hormone (GHRH) neurons- 26% and somatostatin (SS) neurons-1.5 fold, accompanied by higher GHRH and SS staining intensity in the median eminence (ME). However, there is no evidence as to whether D exposure, has the same effect. Using histological and stereological approach we investigated the effects of D on GHRH and SS neurons in the hypothalamus, as well as their content in the ME. The Arc nucleus volume was decreased by 17% following D, in the comparison to G treatment. The same parameter wasn't change after D exposure in comparison to the control value. Also, the periventricular (Pe) nucleus volume was decreased by 15% in the D treated group in comparison to the G group. The Pe nucleus volume wasn't change after D exposure in comparison to the control. The volume density of GHRH and SS neurons within Arc and Pe nucleus respectively, significantly decreased following D in comparison to G treatment. There is no changes in the GHRH and SS staining intensity in ME after D treatment in comparison to the control, while differences was noticed in comparison to the G treatment. The stronger affinity of G for the estrogen receptors is a probable cause of greater changes in the level of the hypothalamus following genistein's treatment vs. daidzein's treatment. Also, the application's method (subcutaneously injected genistein and daidzein) i.e. reduced conversion of D into a more potent equol by enterobacteria, might be the basis for obtained results. Therefore, the eventual changes at the level of hypothalamus should be investigated after feeding experimental animals with isoflavones rich diet.
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P751

Efficacy and safety of a combinated pasireotide lar, pegvisomant and cabergoline treatment in four cases of aggressive somatotrophinomas
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Introduction
A significant number of GH-secreting pituitary adenomas show an aggressive behavior, therefore, when uncontrolled acromegaly persists, a pharmaceutical combination may improve biochemical control, with reduction of disease morbidity and mortality. We aimed to describe the clinical features of four patients successfully treated with a pharmacological combination of pasireotide LAR, pegvisomant and cabergoline.

Case reports
Acromegaly was diagnosed in young age, except for one patient that received diagnosis at the age of 65. Hormonal assays documented impaired secretion of IGF-1 (>1100 ng/ml) and GH (>8 ng/ml), without any suppression at OGTT. Contrasted pituitary and brain MR showed in all cases the presence of a pituitary macroadenoma extending in the cavernous sinuses, optical chiasm, sphenoid sinus and third ventricle. Patients underwent one or two neurosurgical procedures through the transfenoidal approach and, in one case, through the transcranial route. In one patient, neurosurgery was not carried out because of multiple comorbidities. Histological examination demonstrated pituitary adenomas with diffuse immunostaining for GH and, in one case, also for PRL, with Ki67 labelling index >1.5%. Immunohistochemistry for SSTRs subtypes showed in one case high expression of SSTR5 (score 3) and absence of SSTR2 (score 0) and in another case decreased expression of both SSTR 2 and SSTR5 (score 2). According to persistence of high levels of IGF-1 after neurosurgery and after SSAs and DA combined treatment (>1000 ng/ml), pegvisomant was added in increasing dosage up to 30 mg/day, without any important biochemical improvement (IGF-1 >500 ng/ml). Thus, patients suspended conventional SSAs therapy and began pasireotide Lar up to 60 mg/month, with improved disease control (IGF-1 age- and sexed-normalized) and stability of residual tumor mass at radiological evaluation. None of patients had significant adverse effects, particularly worsening of glycemic status.
Conclusions
Treating patients with acromegaly can be extremely challenging, and inadequate disease control may lead to serious consequences. Pegvisomant and combination therapies have been used to manage patients uncontrolled on first-generation SSAs. Several factors can predict poor response to SSAs, such as young age, high tumor size, elevated Ki67 index, reduced SSTR2/SSTR5 and sparsely granulated pattern of tumor. Pasireotide LAR seems to be a promising medical therapy for patients that cannot be controlled with conventional SSAs, accordingly to the pattern of SSTRs expression. Therefore, a multimodal therapeutic approach with pasireotide LAR, cabergoline and pegvisomant can be effective and safe in the management of resistant disease.
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P752

Pediatric hyperprolactinemia: a review of 25 cases
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Objective
Hyperprolactinemia is a rare endocrine disorder in childhood, which may be due to various etiological factors and may present with different signs and symptoms. We aimed to evaluate the etiologic reasons, clinical features and outcome in hyperprolactinemia patients retrospectively.
Method
Data from 25 patients who were followed up with hyperprolactinemia between years 2009 and 2017 were evaluated.
Results
A total of 25 patients [23 female (92%) and 2 male (8%)], with a mean referral age of 15.6±1.2 years were enrolled in the study. The mean duration of follow up was 21.1±11.5 (6-46) months. In 2 patients who presented with pubertal gynecomastia and acne vulgaris, macroprolactinemia (prolactine levels; 47.4 and 47.3 ng/ml) was detected. The most frequent symptoms were menstrual disorders (15 of 23), galactorrhea (7 of 23). Visual field defect was only seen in patients with macroadenoma. All patients were at pubertal stage. The mean prolactin level of the patients ($n=23$), female group ($n=22$) and male group ($n=1$) were 138.6±106.2 (31.5-479), 123.2±79.4 (31.5-315), 479 ng/ml, respectively. Eleven patients had microadenoma, six had macroadenoma, five were diagnosed with idiopathic hyperprolactinemia and Rathke's cleft cyst was found in one. Cabergoline (0.25-0.5 mg/week in one /two doses) were given to all as initial therapy. Treatment was switched to bromocriptine in one because of treatment intolerance. All but one of the patients were responsive to medical treatment, gonadal and neurological functions were normalized. The patient who was unresponsive to medical treatment was male and had macroadenoma (35× 20 mm) secreting PRL and growth hormone. Tumor was invasive to cavernous sinus and causing visual field defect. Surgery was performed as twice and gama knife was also performed for residual tumor and medical treatment(cabergoline and sandostatine) was continued after surgery. Hypothyroidism and hypocortisolemia were developed after treatment. No pituitary hormone abnormality was observed in others. Two patients with macroadenoma, one with microadenoma left follow up. Tumor sizes were not changed significantly in the majority of patients, only in two, tumor regressed totally. Treatment was completed in five, mean treatment duration was 23 (12-36) months.

Conclusion
Hyperprolactinemia should be considered in the differential diagnosis of cases with amenorrhea (primary/secondary), oligomenorrhea, galactorrhea. Medical treatment should be the first-line treatment option in both microadenoma and macroadenoma cases. Surgery should be employed in cases that have cavernous sinüs invasion or signs of nerve compression.

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P753

Could predict the postoperative rosnance the acromegaly cure?

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Acromegaly is caused by excessive growth hormone (GH) secretion from pituitary adenomas. Transphenoidal surgery is the first-choice treatment, but new drug therapies (e.g. somatostatin analogs, SSA) offer promising avenues for medical treatment. Complementary diagnostic tools may assist this strategy, helping to refine drug choice. Here, we investigate the associations between postsurgical radiological features and molecular phenotype of pituitary tumors from acromegalic patients and cure acromegaly. This observational study included 17 acromegaly patients (38.4 ± 15.6 yrs; 64.7% women), diagnosed from 2007 to 2012 at the Endocrinology and Nutrition Unit of the Reina Sofia Hospital, in whom surgery, radiology and molecular phenotyping of the adenoma was carried out. Magnetic resonance was performed to localize the tumors, which were all macroadenomas (94.6%) at diagnosis except for 1 microadenoma. Of the 3 patients who met criteria for cure, the postoperative magnetic resonance was normal (p 0.071). There are no differences in postoperative resonance among patients who had been on treatment with SSA. Of the 13 patients treated preoperatively with PFS, 2 had normal and 11 abnormal postoperative MRI (p 0.730). There are no differences in GH, IGF-1 or nadir GH among patients who had normal or abnormal postoperative MRI. GH preoperative in patients with normal MR were 10.50 ± 4.29 ng/dl, IGF-1 754.19 ± 98.97 and Nadir GH 1.69 ± 0.23 ng/dl, in anormal MR were 7.29 ± 8.11, 576.19 ± 295.76 and 7.02 ± 8.36 respectively.
Conclusion
When the postoperative resonance is normal, the healing is significantly greater.

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P754

Initiation of tolvaptan therapy for mild/moderate chronic SIADH-induced hyponatremia in a day-ward

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Introduction
Tolvaptan is the only V2-receptor antagonist authorized for use in Europe in patients with SIADH. Its initiation requires hospitalization. Our goal was to analyze the safety and efficacy of tolvaptan started in a Hospital Day-Ward.
Material and methods
Retrospective descriptive study of 33 ambulatory patients with mild/moderate SIADH-induced chronic sustained hyponatremia initiating tolvaptan therapy in the Day-Ward of a tertiary center over a 4-year period (2014-2017). Following obtention of Blood/urine samples, 7.5mg of tolvaptan were administered at 08:15AM, with patients instructed to drink freely. Blood/urine tests repeated 6, 24 and 48 hours post-initial tolvaptan dose (ITD). Electrolytes in mmol/L, osmolality(Osm) in mOsm/kg. If serum 6-hour sodium(SNa) rose < 5, patients returned the following morning. "Braking protocol": If 6-hour SNa rose 5 mmol, 3 mcg DDAVP were administered sc; 6 mmol rise: DDVP + 5% dextrose iv 2cc/kg/hour for 2 hours; ≥ 7: DDAVP + dextrose 3cc/kg/hour 3 hours, with patients returning the following morning. "Braked" patients received 7.5mg on day 2, non-braked 15mg, with overcorrection ruled out. A 24h-hour SNa increment > 10 or 48-hour rise > 18 was considered overcorrection. Results as Mean (Standard Deviation) or median [Interquartile range].
Results
Age: 71.7 (9.09). 25/33 women. Principal SIADH etiologies: 11/33 oncological, 6/33 pharmacological, 5/33 neurological. Baseline: SNa 129.6 (2.6), SOsm 270 (7.2), Urine(U) Na 76 [54-118], UOsm 378 [279-519]. 6-hours post-ITD: SNa rose 3.1(2.4). 8/33 presented SNa ascent ≥ 5 and Braking protocol applied. 24-hours post-ITD: SNa rose 3.7 (2.3) from baseline. In 15/33 SNa rose ≤ 2 mmol/L, in 18/33 SNa rose 3-10 mmol/L, with no significant difference between "braked" and "non-braked" patients. No patient presented overcorrection. Men presented a significantly higher 24h-SNa rise than women: 4.9 (2.8) versus 3.2 (1.9) respectively ($P = 0.043$). 48-hours post-ITD: SNa rose 5.55 (2.74) from baseline. 22/33 (66.7%) of patients attained SNa ≥ 135. The maximum 48-hour rise: 12. SNa levels at 6, 24 and 48 hours post-tolvaptan initiation were all significantly higher than at baseline ($P < 0.0001$ in all). Neither initial SNa nor UOsm predicted the 6, 24 or 48-hour SNa increment. No side effects were observed.
Conclusions
Two-thirds of the patients attained eunatremia after 48 hours, with no cases of overcorrection. The protocol is safe and effective for initiation of tolvaptan therapy in a day-ward, avoiding the need for conventional hospitalization in these ambulatory SIADH patients.

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P755

Ki67 as a marker of recurrence in craniopharyngioma

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Craniopharyngiomas (CP) are low-prevalent tumors characterized for their local invasiveness and poor clinical outcomes, often requiring aggressive therapeutic measures. Ki67 is a marker of proliferation with good correlation with tumor recurrence in many solid tumors but this relationship is unclear in CP. Our aim is to determine whether Ki67 could be a marker for recurrence in CP.
Material and methods
Descriptive retrospective observational study. All patients with confirmed histology of CP and tissue sample available for immunohistochemical analysis admitted to the Endocrinology Department from Virgen Del Rocio University Hospital (Seville, Spain) from January 2000 to December 2013 were included. Immunohistochemical analysis for Ki67 was performed on tumor samples following standard procedures. Tumors were in 2 groups according to the Ki67 proliferation index (number of positive cells per high power field score: Group A (Ki67 < 10%) and group B (Ki67 > 10%). Quantitative variables are expressed as Median [Interquartile Range], while qualitative ones are expressed as number of patients/patients with available data (percentage). As all variables followed a non-parametric distribution (Demonstrated by Shapiro-Wilks and Kolmogorov-Smirnov tests when appropriate), Chi-Square, Fisher's exact test and Z-test with Benjamini-Hochberg correction were used when needed. A p-value < 0.05 was considered as significant.
Results
Our study population included 29 patients (12 male and 17 female), with a median age at diagnosis of 28.5 years [IQR7.25-46.00]. 12 were children (under 18 years old), and 17 adults (older than 18). A higher tumor recurrence rate was found in tumors with Ki67 proliferative index > 10%, 8/9 (88.9%) in comparison with Ki67 < 10% (6/15, 40.0%, $P = 0.019$). In children, six tumors display Ki67 < 10% and 6 Ki67 > 10%; recurrences were observed in 2/6 (33.3%) in the first group and in 6/6 (100%) in the second, respectively ($P = 0.061$). In adults, 9 tumors displayed Ki67 < 10% and 3 patients Ki67 > 10% (in 5 patients, no reliable data could be obtained); recurrences were observed in 4/9 (44.4%) in the first group and in 2/3 (66.7%) in the second, respectively ($P = 1{,}000$). There were no differences between age groups.
Conclusions
In our series, CP with Ki67 proliferative index > 10% are more likely to recur; sub-analysis per age group shows the same pattern. These findings support the use of Ki67 as a marker for recurrence in CP.

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P756

Pituitary abscesses diagnosis and therapeutic approach in a reference unit

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Introduction
Pituitary abscess (PA) is a rare condition, representing less than 1% of pituitary lessions. Only around 200 cases have been reported in the scientific literature. Preoperative diagnosis is often challenging due to nonspecific clinical and radiological manifestations.
Materials and methods
Retrospective descriptive cohort study. We analyze demographic and clinical variables, hormonal involvement, recurrence, type of surgery and antibiotic therapy. Data were obtained from electronic health records with patient's informed consent.
Results
Seven cases were found mean age 54 ± 31 years, 71.4% were women and a mean follow-up 4 ± 10 years. At presentation, 100% reported headache, 57.1% (4) exhibited diabetes insipidus and 42.9% (3) had visual impairment. No cases presented with fever and leukocytosis was observed in 57.1%. Three of them (42.9%) were primary abscesses; three developed after pituitary adenoma surgery and 1 after Rathke's cleft cyst surgery, with a mean time between surgery and abscess development of 4 ± 15 years. All of them were submitted to transesfenoidal surgery. Panhypopituitarism was observed in 42.9% (3), ACTH, TSH and FSH/LH in 28.6% (2) and 2 presented isolated GH or TSH impairment. Four patients were diagnosed intraoperatively. Gram cultures were positive in 85.7% (6). The organisms isolated from the cultured material were Staphylococcus Aureus (42.9%, 3), P. Acnes (14.3%, 1) and Corynebacterium (14.3%, 1). Sequential antibiotic therapy with linezolid was used in 42.9% (3). After the initial operative and antibiotic treatment, cure was obtained in 85.7% of the patients and only one recidive of a primary abscess was observed 3 years after the first surgery.
Conclutions
We describe a large cohort of patients compared to the reported cases in the scientific literature. We observed a high cure rate in our serie, with just one case of recurrence, probably due to consecutive surgical and medical treatment.

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P757

Efficacy and effectiveness of pegvisomant monotherapy in treatment patients with acromegaly – systematic review with meta-analysis

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Objectives
The aim of this systematic review was assessment of clinical efficacy of pegvisomant (PEG) in the treatment of adult patients (age ≥ 18 years) with acromegaly.
Methods
The review was conducted according to the Cochrane Collaboration guidelines and polish recommendations of The Agency for Health Technology Assessment and Tariff System. Since acromegaly is a rare disease, not only randomized clinical trials (RCTs), but also real world data (registry, observational studies) were the scope of interest. Calculations (statistical aggregation) were performed using the StatsDirect® 3 statistical package.
Results
One multicenter RCT was identified, which examined the health effects of three doses (10, 15 and 20 mg) of PEG on adults with acromegaly. Further observation (extension phase) was also presented in a period of 18 months. The probability of achieved IGF-1 normalization for PEG 10 mg, 15 mg, 20 mg was respectively 3.97, 7.15, 8.49 higher than in placebo group. After 18 months, 97% of patients achieved normalization. The results from real world data (8 non-RCTs studies) confirm the high effectiveness of the therapy. Calculated weighted average percentages of normalization of IGF-1 after 6 and 12 months and at least 5 years were as follows: 55% (95% CI: 51%, 59%); 60% (95% CI: 56%; 64%) and 69% (95% CI: 64%; 74%).
Conclusions
All the identified scientific evidence confirmed effectiveness of PEG administered as monotherapy in nearly 1,500 acromegalic patients, who did not respond to previous treatment in the long-term follow-up to 11 years of therapy. PEG is currently the only drug, recommended by clinical guidelines for the treatment of acromegaly, that can be offered to treat acromegalic patients, who did not respond well to surgery and/or radiation therapy, and to treatment with somatostatin analogues.

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P758

The occurrence of hyperprolactinemia in a hormonally inactive pituitary adenoma

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Aim
The work was initiated to study prolactin levels in hormonally inactive pituitary adenoma by the size of the tumor.
Material and methods
We examined 85 patients with hormonally inactive pituitary adenomas, 45 women and 40 men among them aged from 18 to 50 years (mean age 44.5 ± 3.85 years). The disease duration from the onset to diagnosis based on the medical history and MRI ranged from 1 to 15 years.
Results and discussion
Guided by the aim of study we divided the patients into three groups. 26 patients with the tumor size up to 10 mm were included into the first group. 33 patients with the tumor size up to 20 mm comprised the second group. 26 patients with the tumor size 30 and more mm were included into the third group. Analysis of hormonal parameters demonstrated correlation between prolactin level and the tumor size. Hyperprolactinemia was registered in 2%, 45% and 100% of patients in the first group, second and third groups, respectively. In patients with macroadenomas hyperprolactinemia was clinically presented in combination with hypopituitarism. Among patients of the third group, chiasmal and cephalgic syndromes, the latter with the oculomotor nerve damage, were the main symptoms; lactorrhea-amenorrhea syndrome came the third.
Conclusions
Quite frequent sign of hormonally inactive adenoma, hyperprolactinemia upon formations in chiasmal-sellar area not always can be an outcome of prolactin-secreting adenomas; the fact is to be taken into account in choosing the treatment tactics.

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P759

Body composition and bone health in patients treated for craniopharyngioma: a retrospective 10 year follow-up study

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Introduction
Craniopharyngiomas are benign tumors in the suprasellar region that have encouraging survival rates between 77-93%. Unfortunately, long-term sequelae are frequent, resulting in excessive endocrine and metabolic morbidity, including premature cardiovascular disease and reduced bone health.
Objective
To determine the prevalence of unfavorable body composition and low bone mineral density (BMD) in patients with craniopharyngioma.
Methods
We studied a retrospective cohort of 93 Dutch and Swedish patients with craniopharyngioma, with at least two DXA-scans available. Outcomes of the first and last available DXA-scans (i.e. BMD, fat free mass index (FFMI), fat mass

index (FMI), and body mass index (BMI)), were expressed as standard deviation scores (SDS) based on age, sex, and country of origin, and compared. The prevalence of osteopenia and osteoporosis (BMD SDS <-1) was also studied.
Results
The cohort included 47 females (51%) and 45 patients with childhood-onset (48%). Mean age at follow-up was 48 years (range 16-78), and mean time between DXA-scans was 10 years (range 0.08 - 23). At presentation, 55 patients had growth hormone deficiency (60%), 40 hypogonadotropic hypogonadism (44%), 58 ACTH insufficiency (63%), 64 TSH insufficiency (70%), and 49 diabetes insipidus (53%). At the first DXA-scan, mean SDS for BMD of the total body was -0.64 (range −4.21–2.40, $n=72$), mean SDS for femur neck was −0.60 (range −4.55–3.80, $n=63$), mean SDS for L2-L4 was −0.64 (range −3.50–3.90, $n=66$), mean SDS for FFMI 0.22 (range −2.98–3.97, $n=59$), mean SDS for FMI 1.50 (range −0.93–5.02, $n=59$), and mean SDS for BMI 1.53 (range −1.71–7.55, $n=80$). Over time, a significant increase was observed for SDS of BMD of the total body (mean difference 0.68 [95%CI 0.38-0.93; $P<0.01$]) and femur neck (mean difference 0.57 [95%CI 0.06-1.09; $P=0.03$]), SDS of the BMD of L2-L4 (mean difference 0.80 [95%CI 0.28-1.18; $P<0.01$]), and SDS of FFMI (mean difference 0.99 [95%CI 0.54-1.44; $P<0.01$]). Correspondingly, the prevalence of osteopenia and osteoporosis of L2-L4 declined from 47% to 34% ($P<0.05$).
Conclusions
Our cohort of craniopharyngioma patients is at risk of unfavorable body composition, reflected by high FMI and BMI, and of decreased bone health, reflected by negative mean values for SDS for BMD. SDS for BMD of L2-L4, femur neck, and total body, as well as FFMI increased over time, while SDS for BMI and FMI did not change. Also, the proportion of subjects with either osteoporosis or osteopenia in their lumbar spine decreased over time.

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P760

Postoperative basal serum cortisol as a predictor of long-term hypothalamic-pituitary-adrenal axis integrity after endonasal transsphenoidal surgery for sellar and suprasellar masses

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Introduction
Endonasal endoscopic transsphenoidal surgery (EETS) for a sellar or suprasellar mass poses potential complications, including transient or permanent hypopituitarism. Adrenocortical insufficiency is especially worrisome given its potentially life-threatening course, if untreated. Usual clinical practice includes administration of perioperative "stress doses" of steroids followed by long term steroid replacement until the hypothalamic-pituitary-adrenal axis (HPA) is reevaluated. High-dose steroid treatment carries potential side effects.
Objective
To determine if post-surgical morning serum cortisol levels can reliably predict development of long-term hypocortisolism (LT-hC), and the risk factors associated with post-surgery LT-hC.
Materials and methods
Retrospective review of patients who underwent EETS from January 2016-December 2017 in our hospital. Data on tumor size, histology, presurgical hormone deficits and baseline hormonal levels were recollected, and logistic regression analysis was performed to calculate the odds ratio (OR) for development of LT-hC. Patients with Cushing's disease were excluded. Morning serum cortisol level was measured on postoperative day-3 (POD3), and replacement steroid therapy was initiated if deemed necessary. Diagnosis of LT-hC was established based on HPA-axis tests at follow-up. An area under the ROC (AUROC) curve was calculated to determine the cortisol level that best predicts the development of LT-hC.
Results
Forty patients underwent EETS for a sellar or suprasellar mass: 67.5% non-functioning adenomas, 20% functioning adenomas, 5% cysts, 5% craneopharyngiomas, 2.5% meningiomas,. A diagnosis of permanent post-surgical hypocortisolism was made in 11 patients (27.5%). Patients who develop LT-hC have masses >30 mm (mean 35±10 mm). The presence of a presurgical hormone deficit was associated with the development of LT-hC ($P<0.05$]; OR 31.99, 18.33 and 18.00 for central hypothyroidism, central hypogonadism and GH deficit, respectively). Conversely, patients who developed LT-hC were more likely to develop a new-onset post-surgical hormone deficit (OR 57.49 and 14.67% for central hypothyroidism and central hypogonadism, respectively). There were no patients with LT-hC who developed permanent diabetes insipidus. The AUROC curve analysis found that a POD3 morning serum cortisol level >11.2 ug/dl yields a 95.65% sensibility, a 58.82 specificity and a 90.91% negative predictive value for ruling out long-term hypocortisolism.
Conclusions
POD3 morning serum cortisol level can predict development of LT-hC. Levels >11.2 ug/dl reliably rule out LT-hC and may help to avoid over-treatment with steroid replacement in most patients who conserve HPA-axis integrity. Patients with large tumor size and other presurgical hormonal deficits have a higher risk of developing LT-hC after EETS.

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P761

Recurrence of hyperprolactinemia after dopamine agonists withdrawal

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Introduction
Prolactinomas are the most common tumors among functional pituitary adenomas and they constitute 40% of all pituitary tumors. Dopamine agonists (DA) are considered the primary treatment of prolactinoma. DA can lead to complete remission (including eradicacion of the tumor), allowing discotinuation of treatment. So far, there aren't clinical criteria with sufficient predictive value for long-term remission.
Objective
To assess the effect of DA withdrawal, the current recurrence of hyperprolactinemia, and posible factors that predict recurrence.
Patients and methods
We evaluated DA withdrawal in 16 patients with prolactinoma who received DA for at least 2 years with normalization of prolactin levels. Factors that predict recurrence were evaluated.
Results
Sixteen patients (fifteen female and one male) aged between 47 and 27 years at diagnosis were analyzed. Seven patients showed recurrence after dopamine agonists withdrawal while nine remained without dissease signs or symptoms. The most frequent indicator of recurrence was asymptomathic hyperprolactinemia (85%).

Table 1 Data of the remission and recurrence groups about sex, sellar adenoma, microprolactinoma and tumoral mass reduction.

	REMISSION (9/16)	RECURRENCE (7/16)	p
SEX (FEMALE)	9/9 (100%)	6/7 (85.7%)	ns
SELLAR ADENOMA	7/9 (77.7%)	5/7 (71.4%)	
MICROPROLACTINOMA	7/9 (77.7%)	5/7 (71.4%)	
TUMORAL MASS REDUCTION >20%	3/8 (37.5%)	4/7 (57.1%)	

Table 2 Data of the remission group about age at diagnosis, baseline PRL levels, PRL levels after treatment, treatment dose and adenoma diameter.

	Remission group		Recurrence group		p
	AVERAGE	±	AVERAGE	±	ns
Age at diagnosis (years)	35.47	8.33	41	6.19	
Baseline PRL levels (ng/dl)	214.94	209.94	333.64	515.84	
PRL levels after treatment (ng/dl)	14.92	12.74	21.70	28.91	
Initial treatment dose (mg/week)	6.28	7.71	2.41	3.33	
Adenoma diameter (mm)	7.74	2.81	10.42	9.18	
Time to treatment withdrawal (months)	36.12	25.62	18.71	14.10	

Conclusions
The sample is too small to achieve significance but baseline tumor size, baseline PRL level, initial treatment dose and time receiving DA seem to predict recurrence. Significant reduction in tumor size, sex and age don't seem to predict the risk of recurrence.

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P762

A case of impaired vision after cabergoline therapy of macroprolactinoma: case report

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Case report
A male 30 years old, presented with a 12-month history of retro-orbital and frontal headache, oppressive type of moderate intensity, which subsides with analgesics. Subsequently, deterioration of bilateral visual fields, predominantly left side, after that was investigated by a neurologist in INCN in January 2013. A magnetic resonance imaginig scan of the brain showed a 45×50 mm pituitary macroadenoma, with suprasellar extension bowing the optic chiasm and cavernous sinus invasion. Initial laboratory: PRL: 6470 ng/mL, patient was treated with prednisone 5 mg qd and LT4 100 ug qd and cabergoline (CBG) 1.5 mg/week for 12 months; with effect on his symptoms, improved vision and headache episodes; after that he was taken CBG irregularly, even suspended for about three months. Six months before admission to ER, presents moderate intensity headache and progressive deterioration of bilateral visual fields predominantly left, therefore CBG were restarted (1.5 mg/week). On admission, severe headache and persistence of visual impairment were reported. MRI showed parietal lobe herniation into sella. Admission lab: PRL: 112 ng/ml, GH 0.05 ng/ml, TSH 1.84 uUl/ml, T4L 0.78 ng/dl, ACTH 17 pg/ml, cortisol 16.8 ug/dl, IGF-1 164 ng/ml. He subsequently underwent a left pterional craniotomy, optic nerve decompression, plasty of bone sellar region. Findings: gyrus rectus-frontal lobe herniation into sella, made marked compression of the optic chiasm and left optic nerve; intrasellar solid tumor with cystic degeneration. In the postoperative, visual fields improve and headaches disappears; PRL: 87 ng/ml, T4L 0.80 ng/dl, IGF-1: 78.8 ng/ml, cortisol 12 ug/dl, thyroid medication continues, and CBG doses diminishes to 1 mg/week.
Conclusions
Prolactinomas on CBG experienced, at least 50% of tumor regression during the first 6 months, but rarely has reported this severe adverse effect of the tumor shrinkage, as in this case, brain or brainstem herniation into sella may occur, depending on the pretreatment tumoral extension. The prompt identification of visual defects should lead to optimization of medical treatment aiming at visual improvement and prevention of further deterioration.

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P763

The levels of serum osmolality, sodium, and copeptin as predictors of the development of postoperative diabetes insipidus

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Objective
To assess the levels of osmolality, sodium in blood and urine, and copeptin level in patients after transnasal adenomectomy for pituitary adenomas.
Materials and methods
A total of 154 patients, aged 18 to 65 years, were included in this study and underwent transnasal adenomectomy. Surgical treatment was performed in 73 patients with Cushing's disease, 66 – acromegaly, 4 – prolactinoma, 9 – hormonally inactive adenoma, 1 – Nelson syndrome, 1 – TSH-oma. Before and after surgery, patients were assessed the sodium levels, blood and urine osmolality, and 30 patients were tested for copeptin.
Results
The development of a permanent form of central diabetes insipidus (central DI) in the postoperative period was noted in 22 patients (14.3%), transient form was detected in 39 patients (25.3%). In 2 patients (1.3%) development of hyponatremia was noted. In 91 patients (59%) there was no development of water-electrolyte disturbances. When assessing the level of blood osmolality in the dynamics of patients of different groups, no statistically significant differences were found ($P > 0.05$), however, when assessing the blood sodium level, significant differences were revealed in the postoperative period in patients with transient DI compared to the group of patients without water-electrolyte disorders ($P = 0.024$ and $P = 0.015$ for 1–3 and 5–7 days of follow-up, respectively), and significant differences in pre- and postoperative sodium levels were found in patients with transient ($P < 0.008$) and permanent form of DI ($P < 0.05$). When assessing the level of copeptin, there were no statistically significant differences between pre- and postoperative levels, but patients with a permanent central DI form had a sharp decrease in its level (median 10.13 (6.181; 10.98) pmol/L before the procedure, 5.265 [4.7, 8.262] pmol/L after the intervention). When assessing the level of osmolality and sodium in urine, significant differences in the indices of osmolality and sodium in patients with a constant and transient form of central DI were found in comparison with patients without disturbances ($P < 0.05$), and significant differences in the level of osmolality of urine in the dynamics in patients with transient form of the central DI ($P < 0.006$).
Conclusions
Blood sodium, osmolality and sodium in urine indicators are sensitive markers for diagnosis and prediction of further development of water-electrolyte disturbances in the early postoperative period. The level of copeptin as a predictor of the development of the permanent form of central DI, is a promising marker for further study.

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P764

Pregnancy outcomes in women with active acromegaly.

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Growth hormone (GH) producing tumors are commonly associated with menstrual disorders and anovulation because of the direct effects of tumor mass on gonadotropins and possible association with hyperprolactinemia. However, some women with acromegaly get pregnant, which rises up a lot of questions about medication, complications and follow-up. We report outcomes of 7 cases of pregnancy in patients with active acromegaly. A median age of patients was 30 years, four of them were with macroadenoma and 3 - microsomatotropinoma. All women had elevated levels of GH and IGF-1 at the period of conception – 7.6 ng/ml [6.1;16.4] and 550 ng/ml [453.7;674.5], respectively. Three patients also had a mild hyperprolactinemia, two women previously underwent transnasal adenomectomy and one – radiation therapy without complete affect. Only three women had regular menstrual function, two had amenorrhea and two – oligomenorrhea. In 57% of cases patients got pregnant during complex therapy with octreotide (mean dose 20 mg per 28 days) and cabergoline (mean dose 1 mg per week), period of treatment before conception varied from 1 to 35 months. Of 7 pregnancies only 5 resulted in births, in one patient, with diabetes mellitus and poor glucose control, a spontaneous miscarriage was registered at 9 weeks of gestation and one woman required medical abortion at 10 weeks due to the episodes of severe hypotension. The average gestational duration was 39 weeks. Preterm delivery occurred in one woman at 24 weeks that led to newborn death, other children were healthy (average height – 52.3 cm, weight – 3332.5 g). These clinical cases demonstrate that women with acromegaly do have a reproductive potential in spite of menstrual disorders and a lot of comorbidities. Pregnancy in active stage of the disease can be complicated by miscarriage and preterm delivery. So preconception counselling and intensive monitoring during gestation is necessary for successful pregnancy and neonatal outcome.

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P765

Rathke's cleft cyst mimiking pituitary apoplexy: a case report

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Introduction
The most common sellar lesions are mainly due to pituitary adenomas, craniopharyngiomas and benign cysts. Rathke's cleft cyst (RCC) is a developmental sellar or suprasellar cystic lesion, which rarely becomes symptomatic. Here, we present an interesting case of intra sellar RCC, with a presenting feature of acute pituitary apoplexy.
Case report
A 39 year old healthy women was referred to the emergency room for sudden headache and fatigue without visual disturbance. Neurological examination was within normal limits and brain CT scan revealed a high density 9 mm area in the sella suggesting a pituitary apoplexy. The patient was hospitalized and treated with hydrocortison infusion. Hormonal profile was within normal limits indicating normal pituitary function. On MRI study, oval slightly hyperintense areas measuring 10-mm were noted on T1 weighted that turned hypointense on T2 weighted sequence. The same lesions were seen in pituitary MRI realized 5 years ago showing stability of the mass which highly suggested the diagnosis of RCC.
Conclusion
RCCs are rarely symptomatic. CT and MRI brain studies are essential in establishing the diagnosis In the presence of apoplectic symptoms. However, it is important to include RCC in addition to pituitary apoplexy in the differential diagnosis.

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P766

Quality of life acromegalic patients based on the AcroQoL questionnaire

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Introduction
Acromegaly is a rare chronic disease caused by growth hormone (GH) and insulin-like growth factor 1 type (IRF-1) excess. However, reaching biochemical control of the disease does not always guarantee the improvement of symptoms that play a significant role in the quality of life associated with human health (HRQoL), in particular, patients with acromegaly.
Goal
To investigate the quality of life in patients with acromegaly in the Moscow region.
Material and methods
The study included 114 patients aged 18 to 83 years (average age 56 years (13.6; 25.2)). All patients were divided into two groups by age - over 50 ($n=77$) and/or under 50 ($n=38$). Also, the patients were divided into groups, depending on the previous treatment. All patients were divided into two groups: uncontrolled current (active acromegaly) and controlled for (acromegaly in remission based on the previously proposed remission criteria. The data are presented as a median (range). Changes in the levels of GH and IGF-1, as well as the AcroQoL score, were analyzed using the Mann-Whitney U test, $P<0.05$ was considered statistically significant.
Results
The quality of life of patients with controlled and uncontrolled disease is no different (or maybe better this way: There is no difference between the QOL in patients with controlled and uncontrolled acromegaly). The IGF-1 level and the percentage of excess IGF-1 significantly correlated with the parameter "personal relationship" ($P=0.026/0.05$). For other hormonal parameters and quality of life significant correlations were not received ($P>0.05$). Surgical treatment and radiation therapy do not affect the QOL of patients, and therapy ASS effect on QOL only in the parameter "physical score" ($P=0.034$). In the group of patients who did not receive treatment earlier, QOL parameters "total score" and "physical score" is higher than in the group of patients receiving therapy.
The conclusion
Treatment either does not affect the quality of life (surgical, radiation, for example) or worsens it. This can be explained by the fact that there are no fast, instantly noticeable results of using modern methods of acromegalic therapy, and complications from them are manifested rather distinctly. As a result, the patient may get the impression that his quality of life has worsened, despite the fact that in the long term the appropriateness of the specific treatment is absolutely proven.
Keywords: Quality of life, acromegaly, IRF-1, GR, register, AcroQoL
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P767

Female patients with acromegaly in Russian hypothalamic and pituitary tumors registry (OGGO)

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Aim
To assess the data of the registry concerning women with acromegaly.
Materials and methods
Russian hypothalamic and pituitary tumors registry database, containing the information on 3968 acromegalic patients.
Results
From all patients with acromegaly registered in the database, 2878 patients (72.5%) are women. We assessed the following data on gonadal status and reproductive function in this group: 512 patients have irregular menses, 117 patients have complaints on low libido, 90 complain of galactorrhea, 71 reported inability to conceive. 26 patients had hypogonadism prior to diagnosis, 60 after pituitary surgery, 15 after pituitary radiation therapy. 44 patient were pregnant during the disease. In the group of patients with active disease ($n=907$), 11% have pituitary microadenomas, 43% macroadenomas, in 46% of patients there is no data regarding current pituitary tumor size. Transnasal transsphenoidal pituitary surgery was performed in 291 patients, 75 patients underwent radiotherapy, 527 and 242 patients are treated with somatostatin analogues and dopamine agonists respectively. Data on disease state is available in 1927 patients (67%): 29.7% have remission, 23.2% have partial remisson, 47.1% have active disease.
Conclusions
Russian hypothalamic-pituitary tumors registry contains useful clinical data on acromegalic patients. However, the data concerning gonadal status and reproductive function is lacking. It could be explained by either low rate of complaints itself or by lack of active assessment by physicians. Thus, it is essential to drive health care practitioners towards more active gonadal status and reproductive function assessment in women with acromegaly, because the rate of reproductive disorders in this group of patients may be higher than in population.

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P768

ACTH-secreting pituitary adenomas surgical outcomes and complications in Endoscopic transsphenoidal pituitary surgery (ETPS)

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Methods
Descriptive retrospective study among patients who underwent ETPS for ACTH-secreting pituitary adenomas performed by the same surgical team from January/2013 to January/2017.
Results
27 ACTH-secreting pituitary adenomas operated via ETPS. 20 (74.1%) were women, median age at surgery was 43.25 [29.65–61.59] years and median follow-up was 3.13 [1.6–6.69] years. Presurgically, 25 (92.59%) patients recieved drugs for control cortisol hypersecretion; all 25 recieved Ketoconazol, in the other 2 (7.41%) the treatment (ketoconazol) was discontinued due to hypertransaminasemia. Median presurgical dosage was 600 [400–600] mg/día. 8 (29.62%) patients were macroadeomas with a median size of 6.55 [5–12] mm. 1 (3.7%) showed a Ki expression >3% and 3 (11.1%) patients showed cavernous sinus invasion. 19 (70.37%) patients were operated by first time, 7 (25.93%) had been previously operated one time and 1 (3.7) had been operated two times before the ETPS aproach. 16 (84.21%) of the first operated patients showed at the end of observation period healing criteria, 2 of them were precociously reoperated due to tumor remains were observed in postsurgical MRI. Among first operated patients

4 were macroadenomas, and all of them were disease-free at the end of observation period; 15 were microadenomas and 12 (80%) were disease-free at the end of the study. After the surgery, 13 (68.42%) developed transient diabetes insipidous, 2 (10.53%) patients thyroid dysfunction, 11 (57.89%) steroid dysfunction and 1 (5.26%) gonadal one. 1 patient showed presurgical campymetric defects which showed an improvement after de surgery. 8 patients operated in this period had been operated previously via transsphenoidal microscopical. At the end of the observation period 6 (75%) patients were disease free. Al complications after surgery in reoperated patients, 1 patient showed a suspected meningitis and hydrocefalus. 3 (37.5%) developed postsurgical DI, 1 (12.5%) steroid dysfunction and 1 (12.5%) thyroid dysfunction.
Conclusions
In our series, ETPS showed better results than microscopic approach if we compare our series with the literature and no further complications were found. ETPS is shown as a very useful thecnique in patients previously operated by a microcopic approach.

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P769

Clinical outcomes and complications in Endoscopic transsphenoidal pituitary surgery (ETPS) for Non-functioning pituitary adenomas

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Methods
We conducted a retrospective descriptive study including 67 patients with non-functioning pituitary adenomas surgicaly removed via ETPS beetwen January/2013 to January/2017.
Results
Among 67 patients with non-functioning pituitary adenomas surgicaly removed via ETPS 44 (65.67%) were men. 52 (77.61%) patients recieved their first surgery, 14 (20.9%) had been operated one time before and 1 (1.49%) had been operated two times. Every patient reoperated had been previously operated by transsphenoidal microscopic approach before ETPS. Presurgical median age was 55.53 [44.09–69.38] years and median follow-up was 3.67 [2.25–5.69] years. Presurgically, 37 (56.06%) patients showed thyroid dysfunction, 18 (27.27%), steriod dysfunction, 41 (62.12%) gonadal dysfunction and 25 (37.88%) somatotropic deficiency. 16 (23.88%) adenomas were null cell, 11 (16.42%) silent corticotroph, 3 (4.48%) silent somatotroph (1 showed PRL cosecretion), 2 PRL (2.99%), 1 (1.49%) TSH, and the other were gonadotroph adenomas. 6 (8.96%) showed Ki$>$3%. Median utmor size was 27 [21.7–33.7] mm, 45 (67.16%) showed a size $>$25 mm and 29 (43.28%) Knosp 3–4. 52 (77.61%) were operated by first time. 36 (69.23%) patients showed healing criteria at the end of observation, 4 (7.69%) tumor remaining $<$1 cm and 11 (21.15%) had tumor remaining $>$1 cm. Among 23 patients with Knos 3–4, 13 (56.52%) showed healing criteria. Every patients with tumor remains $>$1 cm were adenomas $>$25 mm, 10 (90.9%) showed cavernous sinus invasion. 33 (63.46%) showed presurgical campymetric defects; 21 (63.63%) resolved completely their campimetric defects, 10 (30.3%) showed a partial resolution and no changes were found in 2 (6.06%) patients. After surgery, transient diabetes insipidous was diagnosed in 15 (28.84%) patients, DI permanent in 2 (3.85%), transient SiADH was found in 3 (5.77%). Among patient without hormone involvement, 8 (34.78%) developed a steroid deficiency and 9 (42.86%) gonadal defect. 1 suspected meningitis was observed. Among reoperated patients. 6 (40%) had healing criteria, 3 (20%) tumor remaining $<$1 cm and 6 (40%) tumor remaining $>$1 cm. 1 patient showed a meningitis. As complications 1 patient presented a suspected meningitis. 7 (46.67%) patients had campimetric defects, after surgery 1 (14.29%) resolved completely their campimetric defects, 6 (85.71%) showed an improvement. After surgery, among patients without endocrine involvement, 3 (42.86%) presented thyroid deficiency, 3 (33.33%) steroid, 1 (25%) gonadal deficiency.
Conclusions
In our series, ETPS have shown better outcomes than transsphenoidal microscopic approach if we compare our series with the literature. This approach leads to complete curation in patients with sinus involvement.

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P770

Somatostatin analogues therapy of clinically non-functioning pituitary adenomas- impact on tumour volume and visual field

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Introduction
Surgery remains the first-line treatment of clinically non-functioning pituitary adenomas (NFPA). However, the presence of somatostatin receptors (SSTR) in these tumours forms the basis of clinical use of somatostatin analogues (SSA). Visualisation of SSTR in scintigraphy is compulsory to introduce SSA therapy in NFPA.
Aim
To assess the effectiveness of long-term somatostatin analogues treatment on tumour volume and visual field in patients with NFPA.
Material and methods
Twenty five patients with diagnosed NFPA and strong expression of SSTR in scintigraphy were enrolled in the study. Patients were divided into 2 subgroups: subgroup A, which comprises 8 patients treated with SSA in primary therapy and subgroup B including 17 patients treated with SSA after incomplete surgery. All patients received octreotide LAR 20 mg or lanreotide 120 mg every four weeks and the duration of therapy varied from 7 months to 14 years. Patient's condition, tumour size, visual field and undesirable effects were evaluated in the study.
Results
Almost 70% of patients felt clinical improvement in headaches, which occurred less frequently and were less intense. Stabilisation of tumour size was achieved in 60% of patients. Reduction of tumour volume was only observed in patients treated with SSA as adjuvant therapy after incomplete surgery (23.5% of subgroup B). Adenoma shrinkage was not always associated with improvement in the visual field. Tumour progression was noted with similar frequency in both subgroups (25% subgroup A vs. 23.5% subgroup B). Tumour enlargement correlated with deterioration of visual field. Moreover, an increase of adenoma size was observed within first 2 years of the therapy, while tumour shrinkage occurred 3–5 years after introduction of SSA treatment. SSA were well-tolerated and only four patients developed asymptomatic cholelithiasis during the pharmacotherapy.
Conclusion
SSA are effective in both primary and secondary therapy of NFPA. Long-term treatment with SSA results in stabilisation of tumour size in the majority of cases. SSA therapy should be considered in postoperative treatment of NFPA as tumour shrinkage may be observed in some cases.

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Paediatric Endocrinology

P771

Therapeutic results of growth hormone substitution in children monitored for a growth hormone deficiency: about a Tunisian population

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Introduction
Many problems hinder the diagnostic and therapeutic approach of growth hormone deficiency (GHD) in developing countries. The lack of early diagnosis and adequate treatment have adverse consequences, especially the small final height with the resulting psychological impact. Our study examined 40 cases of GHD who received treatment by recombinant human Growth Hormone (rhGH).
Patients and methods
This is a retrospective longitudinal study of 40 cases of GHD collected in the pediatric department of Mahdia between 1994 and 2014.
Results
The mean chronologiacal age (CA) at the start of treatment was 9.91 ± 0.55 years with an average processing times of 10.37 ± 1.99 months. The mean duration of treatment for all patients was 3.3 ± 0.3 years. At the time of this study, 60% of patients (group A) still received rhGH, 17.5% of patients (group B) defaulted from follow-up and 22.5% of patients (group C) completed their course of rhGH after an average treatment duration of 3.95 ± 0.91 years. Among these patients (group C), four had a 15 year bone age, two had reached their mid-parental height (MPH), one patient had a growth height less than 2 cm/year, and one patient received treatment for only 12 months because of medical insurance problems. The final height (after treatment completion for group C and at the last check up for group B and A) was between -2 s.d. and the mean height in 54.2% of patients

in group A, in 57.2% of patients in group B and in 66.7% of patients in group C. This corresponds to a height outcome of 0.95 s.d. ±0.14 in group A, 0.71 s.d. ± 0.42 in group B and 1.33 s.d. ±0.23 in group C. Thirty-three point three percent of patients in group C were able to reach their MPH. There were a strong correlation between the height outcome and the mean duration of treatment, the CA at the start of treatment and the height at the start of treatment. This implies earli diagnosis, early treatment and a regular follow-up.
Conclusion
The initial approach to rhGH substitution focused on growth only and ended once adult height was reached. But monitoring children with GHD has revealed the need to define the factors that predict the persistence of this deficit in adulthood and the need to continue the treatment.

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P772

GH deficiency in children

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Introduction
GH deficiency (GHD) is a rare etiology of late growth. Its exact prevalence is unknown in emerging countries such as Tunisia. Despite a very suggestive clinical presentation, the diagnosis of GHD remains difficult and relatively late in some patients. Our study examined 40 cases of GHD in the Sahel region of Tunisia.
Patients and methods
This is a retrospective longitudinal study of 40 cases of GHD collected in the pediatric department of Mahdia between 1994 and 2014.
Results
The mean age at diagnosis was 8.31±0.56 years with a sex ratio of 2.07. The mean height at the first visit was 111.38±2.99 cm. The mean bone age (BA) at the time of diagnosis was 5.12±0.5 years. The delay of BA over the chronological age was of 3.41±0.38 yearson average. the diagnosis of total GHD was found in 65% of patients and partial GHD in 35% of patients. Magnetic resonance imaging of the hypothalamic-pituitary region was normal in 60% of patients. Pituitary stalk interruption was observed in 10% of patients, an empty sella was observed in 7.5% of patients, a pituitary hypoplasia was observed in 5% of patients and a posterior pituitary ectopia was found in 5% of patients. The karyotype was only done in 6 patients. Five patients had a normal karyotype 46,XX and only one patient had a karyotype 46,Xi(Xq). The association of Turner syndrome and GHD has already been reported in the literature. Three patients had pubertal delay at the time of diagnosis. The diagnosis of simple pubertal delay was retained in two of them, while it was very likely a pubertal delay secondary to hypogonadotropic hypogonadism in the third.
Conclusion
Despite a very evocative clinical picture, the diagnosis of GHd remains difficult and relatively late in some patients. This delay is explained by the lack of knowledge of the pathology and by the absence of anthropometric monitoring.

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P773

Re-evaluation of GH secretion during the transition age in patients with childhood-onset isolated GH deficiency (IGHD) after GH therapy (GHRx)

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Objectives
GH in addition to promote linear growth during childhood influences several key metabolic processes as well. In the transition period, from late adolescence to early adulthood, GH plays an important role in skeletal mineralization and muscle mass maturation as well as in developing a favorable cardiometabolic profile. Therefore, several lines of evidence propose GH replacement to be continued if GH evaluation at the transition age fulfills established criteria. The aim of this study was to evaluate GH secretion of patients with childhood-onset isolated GH deficiency (IGHD) at transition age.
Methods
Twenty two patients with childhood-onset IGHD [15 males; age 16.1 years (±1.4)] were re-evaluated for GH secretion (using clonidine or glucagon stimulation test) and a GH peak <5 ng/ml was used for the diagnosis of GHD at the transition phase at least four weeks after discontinuation of therapy.
Results
Seven patients out of twenty two with childhood-onset IGHD [5 males; age 16.5 years (±1.6)] (31.8%) were GHD at retesting. Main characteristics of IGHD patients at diagnosis and IGHD or GH-sufficient (GHS) patients at the end of GHRx are shown in Table 1.

Table 1

Characteristics of the patients*	IGHD at diagnosis (n=22)	IGHD in transition (n=7)	GHS in transition (15)
Age at diagnosis (years)	9.6 (2.8)	8.6 (3.1)	10.1 (2.6)
Sex (M: F)	15:7	5:2	10:5
Height (cm)	127.9 (13.1)	120.5 (12.3)	131.5 (13.1)
Target height (cm)	166.6 (6.8)	167.9 (6.7)	166.1 (7.1)
GH peaks at diagnosis 1st test	5.79 (2.7)	6.3 (2.6)	5.5 (2.8)
2nd test	5.12 (2.5)	5.1 (2.3)	5.1 (2,6)
< 5 ng/ml	1st test: 10 2nd test: 9	7	0
5–10 ng/ml	1st test: 12 2nd test: 13	0	11
>10 ng/ml		0	4
Age at the GH re-evaluation (years)	16.1 (1.4)	16.5 (1.6)	15.9 (1.3)
GH peak at the end of GHRx (ng/ml)	7.3 (3.8)	2.8 (1.4)	9.3 (2.6)
Height at the end of GHRx (cm)	162.8 (9)	163.4 (11.7)	162.5 (8.1)

*Values are means ±s.d.

Conclusions
This study demonstrates that one third of childhood - onset IGHD persists during the transition period. Discontinuation of GH therapy may have unfavorable outcome regarding bone density, body composition and lipid profile. Substitution therapy with appropriate adult dosing should be considered.

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P774

Maternal uniparental disomy of the chromosome 14: a case report of mosaicism

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UPD is a congenital disease characterized by the presence of two homologous chromosomes inherited from one parent in a diploid offspring. Its effects can be dramatic when the expression of essential genes is lacking. This is due to a phenomenon known as *genomic imprinting* where only one of the two chromosomal copies is active, depending on the parent of origin. Maternal uniparental disomy of the chromosome 14 (UPD 14 mat) is a rare disorder characterized by prenatal and postnatal growth retardation, neonatal hypotonia, feeding difficulty, motor development delay, mild to moderate intellectual disability, mild facial dysmorphism, truncal obesity, small hands and feet, short stature and precocious puberty. Here we report a case of mosaic UPD(14)mat. G.N. is a girl born to a healthy mother with negative family history for genetic diseases. She was delivered at 37 weeks. Birth weight was at 20th centile, height at 18th centile. She displayed feeding difficulty and week sucking, hypotonia, micrognathia, low-set ears, hypertelorism, open foramen ovale, agenesis of the left hand. At the age of one year she practiced genetic examination with evidence of mosaicism 47XX+mar/46XX; so, she was diagnosed with UPD 14 mat. At the age of 6 years, she came to our Clinic for precocious puberty and growth rate reduction (−2 SD). Height was at 25th centile, weight at 3th centile, Tanner stage B2PH3. She presented with normal motor development and intellectual ability. Her physical features were normal; her craniofacial features included minimal ocular hypertelorism and slightly depressed nasal bridge. ECG, ultrasound thyroid and abdominal examinations were normal. The uterus had normal length and ovaries multiple sub-centimetric follicles. Bone age was 7 years. MRI displayed a normal pituitary gland. All the following hormones were in the normal range for gender and age: LH, FSH, 17BEstradiol, Testosterone, TSH, IGF-1. Tests by Arginine and Clonidine showed a pathological GH peak value while GnRH test demonstrated a puberal peak values of gonadotropins; so the patient was diagnosed with growth hormone deficiency (GHD) and precocious puberty.Therapy with Triptorelin and rhGH was prescribed. After six months,

therapeutic efficacy was confirmed because the patient's height increased by 5.5 cm and there was no progress of her secondary sexual characteristics. This is the first case described in UPD (14) mat in the form of a mosaic. Mosaicism limited the clinical features while some somatic defects and endocrinological disorders persisted. Therapy applied was effective at control after one year.

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P775

Final height in cancer survivors undergoing treatment with somatotropin

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Somatotropin is essential not only for linear growth but also for important metabolic functions. Its deficiency is usually the first and most common endocrinopathy induced by cancer disease and its treatments, mainly cranial irradiation. Although somatotropin replacement therapy is safe and effective in promoting a better linear growth, studies of final height in childhood cancer survivors treated with somatotropin are limited. This study was performed to examine growth outcomes in these patients. A retrospective analysis was performed, through consultation of the clinical processes. We included all childhood cancer survivors treated with somatotropin in a pediatric endocrinology department, between 1988 and 2016. Statistical analysis was performed using SPSS v24. Were included 28 cancer survivors, 64.3% male. The median age at cancer diagnosis was 5.6 years and 60.7% had central nervous system tumors; 60.7% undertook surgery, 71.4% radiotherapy and 67.9% chemotherapy. Only 42.9% had IGF1 more than 2 SDS below the mean, being the most frequent criteria to investigate somatotropin deficiency the height velocity more than 3 SDS below the mean. There were concomitant endocrinopathies in 50% of patients. Somatotropin treatment was started at a median of 11.3 years. The initial height was -2.14 SDS and increased to -1.81 SDS by 1 year, -1.68 SDS by 2 years, and -1.56 SDS by 3 years with somatotropin treatment. There were differences between the initial height and by 1 year ($P<0.001$), by 1 and 2 years ($P=0.006$) and between initial and final height ($P=0.025$). Despite that, this patients' adult height was significantly lower than the midparental height ($P=0.006$). The body mass index decreased, significantly in the first year of treatment ($P=0.002$). The initial IGF1 concentration was -2.02 SDS and increased significantly to 0.93 SDS by 1 year ($P<0.001$). The differences between chronological and bone age decreased throughout the treatment with a significant difference between the beginning and the third year of treatment ($P=0.047$). Median treatment duration was 4.0 years (min 6 months, max 11 years). Difference between adult height and midparental height was not associated with gender, group of tumor, concomitant endocrinopathies, age or puberty stage at beginning. We concluded that the improvement of linear growth was significant, mainly in the first year of treatment, but these patients did not achieve their genetic potential for height. The physicians must be aware and search for this endocrinopathy in this group of patients and treatment should be started as soon as possible.

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Pituitary - Basic

P776

Pregnancy and hypopituitarism: clinical aspects and outcome

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*Equal contribution.

Introduction
Pregnancy in hypopituitary women is a rare and poorly studied clinical condition. Management difficulties and obstetrical complications have been associated with this condition.

Objectives
To define the characteristics, follow-up and perinatal outcomes in hypopituitary pregnant women attended at our centre.
Methods
The clinical data of the hypopituitary pregnant women (deficiency of two or more pituitary hormones), and details on delivery and the newborn are collected prospectively. Here we present eight pregnancies in seven women who had been diagnosed with hypopituitarism before pregnancy.
Results
The median age of the patients was 35 years; hypopituitarism had been diagnosed a mean of 19.5 years prior to pregnancy. The cause of hypopituitarism was pituitary agenesis in two patients, macroprolactinoma in another 2, 1 corticotroph adenoma, 1 hypophysitis, 1 empty sella and 1 granular cell tumour. All pituitary tumours had undergone surgery, but none had received radiotherapy. At the beginning of pregnancy, no patient presented hormonal hypersecretion. There were 7 GH and GnRH deficits, 6 of TSH, 3 of ACTH and 2 of ADH. Five women with GH deficiency had received GH substitution therapy. Six women required assisted reproduction techniques (4 controlled ovarian stimulation, 1 intrauterine insemination, 1 *in vitro* fertilization). During pregnancy, GH replacement was stopped, hydrocortisone dose was maintained, whereas levothyroxine and desmopressin doses were increased. One patient developed *de novo* diabetes insipidus. No acute complications were identified. Gestational age at birth ranged from 36^+ to 42^+ weeks; five patients required labour induction. Delivery was by caesarean section in five cases and vaginal in 3. No foetal distress occurred. Average weight of the newborns (five girls, three boys) was 3200 g and the 5 min Apgar score was 9. No relevant perinatal complications were observed. Four patients experienced a milk surge.
Conclusion
The perinatal outcome of this group of patients with hypopituitarism was satisfactory. It is important to keep in mind the possibility of *de novo* hormonal deficiencies during pregnancy.

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Functional analysis of aryl hydrocarbon receptor (AHR) polymorphisms in pituitary adenomas (PAs) in the presence of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

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Background
PAs are the most frequent pituitary neoplasms, however molecular pathogenesis is largely unknown. The AHR is a ligand-activated transcription factor that regulates expression of various genes that mediate cellular response to xenobiotics. The exact functional role of two AHR single nucleotide polymorphisms (SNPs); Arginine554Lysine (Arg554Lys) and Valine570Isoleucine (Val570Ile) has not yet been established, however studies suggest that these mutations might increase risk of developing PAs. To date, functional analysis of regarding the significance of these AHR SNPs in pituitary pathophysiology has never been analysed.
Aims
- Elucidate the effect of wildtype and polymorphic AHR on GH3 cell proliferation and on AHR-transcriptional response in the presence and absence of TCDD.
- Determine the allele frequency of the most common AHR SNP; the Arg554Lys in PA patients and in a small cohort of the Maltese population.

Method
The two missense mutations were introduced within the AHR-expressing vector and transfected in GH3 cells by magnetofaction, followed by the exposure to TCDD. Cell viability of GH3 transfected cells was measured using the MTT assay. Functional analysis of GH3 transfected cells treated with TCDD was carried out using luciferase assay and real-time PCR to detect and quantify the AHR-transcriptional activity. Genotyping of the Arg554Lys was performed on PA patients and neonatal controls using allele specific PCR. The Mann-Whitney test was used to compare two groups and Kruskall-Wallis test was used to compare three groups or more.
Results
In the absence and presence of low TCDD concentrations (1 and 10 nM), overexpression of wildtype AHR (wtAHR) did not affect GH3 cell proliferation. GH3 cells transfected with the AHR mutants did not exhibit any significant differences in their proliferative ability when compared with the wtAHR, both in the presence and absence of TCDD. Luciferase reporter analysis showed that there was a significant difference between the treated and untreated wtAHR ($P=0.016$), however this difference was not observed between the treated and untreated AHR mutants. Statistically significant difference in *Cyp1a1* gene expression analysis

was detected between the treated and untreated wtAHR ($P=0.021$), Arg554Lys ($P=0.005$) and Val570Ile ($P=0.054$). Genotyping of the Arg554Lys in patients with PA gave a minor allele frequency (MAF) of 3% vs 0% in neonatal controls.
Conclusion
Gene expression and quantification analyses of AHR-target genes suggests that these AHR mutants might interfere with AHR target gene expression. Genotyping results suggested that this mutation is quite rare and may be similar to the frequencies of other European populations.

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Comparative differential effects of secretagogues upon regulation of pituitary GH in several vertebrates

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It is known that the synthesis and release of pituitary GH is controlled by complex neuroendocrine mechanisms that involve several neuropeptides, such as GHRH, SST, PACAP, TRH, GnRH, Ghrelin, among other regulators. Previous reports indicate that, during vertebrate evolution, the potency and efficacy of these secretagogues may vary and play differential effects upon GH regulation. In this work we aimed to study, *in vitro*, the capacity of these peptides to control the expression and secretion of pituitary GH in three vertebrate models: rat (mammals), chicken (birds) and iguana (reptiles), employing pituitary cultures at different incubation periods (0–6 h) and two doses of the secretagogues (1 and 10 nM). Results showed that GHRH significantly stimulated GH mRNA expression as well as GH secretion in the three species within the first hour of incubation, in comparison to the controls. However, its effect upon GH mRNA was 60 times greater in iguana than in the other species. TRH had no effect on GH secretion in any incubation period, but it stimulated GH mRNA expression in all species and, in the case of iguana, its effect was 150 times higher than in the others. PACAP stimulated GH mRNA expression at 4 h in chicken pituitary cultures, whereas no significant differences were observed in rats and iguanas. Ghrelin increased GH secretion in chickens, but had no effect in its mRNA synthesis, contrary to what was found in iguana cultures where GH mRNA significantly diminished. GnRH stimulated both GH mRNA expression and GH release in chicken pituitary cultures, while in iguana only GH secretion was significantly increased. On the other hand, SST strongly inhibited GH mRNA expression and GH release in the iguana, while no significant effect was directly observed in rats and chickens, at the doses and time-frame conditions employed. Results indicate that there is a differential effect of these secretagogues upon GH synthesis and secretion during vertebrate evolution, and further studies are needed to understand how these mechanisms have evolved.

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Next generation sequencing for characterization of mitochondrial genome in pituitary adenomas

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Introduction
Disrupted mitochondrial functions and genetic variations of mitochondrial DNA (mtDNA) have been observed in different tumors. Regarding pituitary adenomas mtDNA was evaluated only in oncocytic type using PCR based methods and it showed high prevalence of Complex I variants. Next generation sequencing (NGS) allows high throughput sequencing and it is useful for accurate identification of heteroplasmy of mitochondrial genome as well.
Aim
We aimed to investigate the entire mitochondrial genome in different adenoma types.
Material and methods
We collected 22 gonadotroph (GO), 11 GH producing (GH) and 11 null-cell (NC) adenoma specimens from samples removed by transsphenoidal surgery. From fresh frozen tissues DNA extraction was performed using QIAamp Fast DNA Tissue Kit. For library preparation VariantPro Amplicon Mitochondrion Panel kit was used. The total mtDNA (16569 bp) was sequenced on Illumina MiSeq Instrument. Following complex bioinformatic analysis Revised Cambridge Reference Sequence (rCRS) of the human mitochondrial DNA was used as reference. Heteroplasmy was determined using 3% cutoff.
Results
The whole mitochondrial genome were covered by 630 ± 370 (avg $\pm$ S.E.) reads per base. 496 variants were identified in adenomas compared to reference sequence. Overall a low (7.22%) heteroplasmy prevalence was found. Based on mitochondrial sequence variants by hierarchical cluster analysis we could not discriminate different adenoma types. No association between Ki-67 index or recurrent-nonrecurrent status of adenomas and mitochondrial variants were detected. Four variants appeared more often in null-cell adenomas compared to gonadotroph adenomas (chrM_188: 18% vs 0%, chrM_16093: 18% vs 0%, chrM_185: 27% vs 0% and chrM_14798: 36% vs 5%; Padj = 0.0246, 0.0246, 0.01542 and 0.01829, respectively). Of these variants chrM_14798, chrM_4216 and chrM_15452 are non-synonymous polymorphisms leading to amino acid change in MT-CYB (mitochondrially encoded cytochrome b) and in MT-ND1 (mitochondrially encoded NADH dehydrogenase 1) genes. We identified chrM_16189 variant (non-protein coding variant) in 40% (6/15) of nonrecurrent adenomas compared to recurrent ones where this variant was not present (0/11) ($P=0.0209$).
Conclusions
Next-generation sequencing is a reliable method for investigating mitochondrial genome and heteroplasmy in pituitary adenomas. In pituitary adenomas the prevalence of heteroplasmy of mitochondrial genome is low suggesting that these alterations may not influence mitochondrial function considerably. Of pituitary tumours only null cell adenomas possess alterations of mitochondrial genome with potential functional consequences suggesting that during the development of this subtype of pituitary tumours mitochondrial function-associated mechanisms may have role.

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P780

Pituitary cell activation and recruitment in hipothyroidism

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Pituitary stem cells have been characterized in the postnatal pituitary. We now know they are organized in a niche and co-express specific markers such as Sox2, Sox9 or Gfra2. Although many studies by our group and others have been dedicated to its characterization *in situ* it is under discussion their role in the maintenance and turnover of the pituitary in physiological conditions or physiological pituitary challenges. It's not known if the stem cells are required and which molecular mechanisms are implicated in recruitment/differentiation. We established a model of hypothyroidism in rodents similar to human conditions in which levels of thyroxine are maintained just below the lower normal cut-off. We studied pituitary extracts in a precise time-course for stem cell and differentiation markers of thyrotropes. We have found that Shh is increased immediately after the establishing of the hypothyroidism. Following this, we purified the Gfra2+ stem cell population from vehicle and short-term hypothyroid animals and grown them as spheres in absence of serum. Spheres grow during the days of culture duplicating from day 1 to day 5 when they reach a plateau. Gfra2+ cells obtained from hypothyroid animals produce a significantly higher level of spheres per well both at day 1 and at day 5. When cultured in presence of cyclopamine, a Shh inhibitor, the number of spheres is significantly reduced in the hypothyroid Gfra2+ but not in the control wells. We used immunofluorescence techniques to see what happen in the intact pituitary niche in vivo. A genetic mouse model of tracing where Gfra2/Sox2 positive cells are induced to express GFP long-term after the tamoxifen injection was followed in a time-course under the same conditions of above vehicle/hypothyroidism. There was a significant increase of the Sox2 positive cell in long-term hypothyroid mice compared with vehicle treated. Tracing the GFP+ population through a time-course, we detected a significant increase in the double GFP/TSH+ cells in the adenopituitary of hypothyroid mice compared to vehicle treated. This data confirm that Sox2 positive cells recruited from the pituitary niche are able to

differentiate into TSH producing cells. In summary, our results indicate that the Gfra2/Sox2 population, the pituitary stem cells, are activated when a mild hypothyroidism is induced. Results *in vitro* and *in vivo* confirm that initially (short-term hypothyroidism) the stem cells are driven to proliferate and expand while later (long-term hypothyroidism) differentiate into thyrotropes.

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P781

SOM230 exerts anti-proliferative actions by reducing phospho-ERK1/2 levels in ACTH-secreting pituitary tumour cells

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Currently, the multi-ligand somatostatin (SS) analogue pasireotide (SOM230) is the only pituitary-targeted drug used to treat patients with Cushing's disease. SOM230 displays the highest affinity to somatostatin receptor type 5 (SSTR5) and compared to octreotide resulted more effective in reducing ACTH release. Despite its anti-secretory role, SOM230 has been associated with tumor shrinkage in patients subjected to long term treatment, although to date the key factors involved are poor elucidated. The present work aimed to investigate the molecular mechanisms implicated in SOM230-induced cytostatic and cytotoxic effects in ACTH-secreting primary tumour cultures and murine corticotroph tumour cells line, AtT-20. First, by western blot we found SSTR5 expressed at comparable levels in 17 different ACTH-secreting pituitary samples, whereas SSTR2 was detectable in 15 out of 17 tissues. SSTR5 and SSTR2 were expressed in AtT-20 cells. Then, we tested the effect of 96h stimulation with 1 μM SOM230 on cell proliferation in 6 different ACTH-secreting tumors by measuring 5-bromo-20-deoxyuridine incorporation during DNA synthesis. We found a significant *in vitro* suppression of cell growth in half of the analyzed samples ($-12.1 \pm 4.3\%$, $P<0.01$). Accordingly, SOM230 significantly inhibited cell growth in a dose-dependent manner in AtT-20 cells ($-10.5 \pm 7.7\%$ at 10 nM, $P<0.05$; $-3.9 \pm 10.9\%$ at 100nM, $P<0.05$; $-26.8 \pm 8.9\%$ at 1 μM, $P<0.01$), whilst octreotide was effective only at 1 μM ($-13.3 \pm 9.1\%$, $P<0.05$). To investigate whether direct antiproliferative actions SOM230-mediated might involve MAPK and cyclins pathways, we evaluated the expression level of phospho-ERK1/2 and CD1 in ACTH-secreting primary cultures exposed to 1 μM of SOM230. SOM230 reduced phospho-ERK1/2 levels in 5 of 8 tumours tested ($-36.4 \pm 20.5\%$, $P<0.01$), whereas no significant difference was found in CD1 expression levels in 3 tumours. These data were further confirmed in AtT-20 cells, where octreotide did not have any effect. Furthermore, we found that 48h incubation with 1 μM SOM230 was able to induce a significant increase of caspase 3/7 activity in 2 of 4 ACTH-secreting primary cultures ($17 \pm 3.6\%$, $P<0.05$). Altogether these data suggest a downstream implication of phospho-ERK1/2 inhibition in ACTH-secreting pituitary tumour cells by SOM230 resulting in cell proliferation suppression and indicating that broader-spectrum SS analogues may play a crucial role in the treatment of tumours where the MAPK pathway is overactivated. Moreover, we describe a pro-apoptotic effect of SOM230. Ongoing experiments are aimed to discriminate the specificity effects played by SSTR5 and SSTR2.

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P782

Factors associated with SF1 gene expression in clinically non-functioning pituitary adenomas

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Clinically non-functioning pituitary adenomas (NFPAs) are a heterogenous group of tumours including silent secreting (somatotroph, corticotroph, rarely lactotroph), as well as gonadotroph (Gn-PA) and null cell (nc-PA) adenomas. These are usually identified by immunostaining for pituitary hormones, though an increasing role for pituitary transcription factors is being recognized for the identification of pituitary cell lineage. The *Steroidogenic Factor 1* (SF1) is involved in gonadotroph differentiation. In addition to Gn-PA, most nc-PA are currently believed to be of gonadotroph origin. SF1 also plays a role in adrenal development and overexperession of SF1 has been reported in adrenocortical tumours.

Aim of the study

To identify factors associated with SF1 gene expression in NFPA.

Material and methods

Twenty-nine NFPA (23 Gn-PA, 6 nc-PA) were selected for SF1 semi-quantitative gene expression by Real-Time RT-PCR analysis after preliminary RT-PCR for Tpit and Pit-1 gene expression, in order to exclude normal pituitary contamination and tumours arising from other pituitary cell lineages. RNA was extracted from surgical samples placed in a RNA later solution before freezing at $-80°C$ until processing. Genes encoding βFSH, βLH, Cyclin D1, Cyclin B1, Caspase 3, Aryl hydrocarbon Interacting protein (AIP) and the dopamine 2 receptor (D2R) were also measured semi-quantitatively. Beta-actin was used as a house-keeping gene. Non-parametric statistical analysis was performed using Wilcoxon and Spearman tests.

Results

SF1 gene expression was significantly higher in Gn-PA than in nc-PA ($P=0.0166$), with no difference between male ($n=20$) and female ($n=9$) tumours. No significant variations in SF1 was found according to tumour invasiveness, maximal tumor diameter, Ki67 index, Cyclin B1, Cyclin D1 or caspase 3 expression. SF1 was strongly correlated with βLH expression ($n=0.77$, $P<0.0001$ in the whole series, $n=0.71$, $P=0.0001$ in Gn-PA) whereas correlations with βFSH only approached significance ($n=0.37$, $P=0.0502$ in the whole series, $P=$ns in Gn-PA). A positive correlation was also observed between SF1 and AIP ($r=0.52$, $P=0.0038$ in the whole series, $n=0.47$, $P=0.023$ in Gn-PA) and in particular with D2R expression ($n=0.67$, $P<0.0001$ in the whole series, $n=0.56$, $P=0.007$ in Gn-PA).

Conclusion

SF1 is a marker of gonadotroph differentiation in NFPA and its expression is significantly correlated with βLH, AIP and D2R. In contrast, it does not appear to be influenced by patients gender or by tumour volume or aggressiveness. The potential implications of SF1 expression in NPFA should be further evaluated.

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P783

Corticotroph pituitary adenomas: the functioning vs the silent: a gene expression study comparing differentially expressed genes in the regulation of POMC

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Background

The exact mechanism behind the hypersecretion of ACTH and lack of negative cortisol feedback on POMC regulation in functional corticotroph adenomas (FCA) is unknown. Silent corticotroph adenomas (SCA) express, but do not secrete functional ACTH and have lower POMC expression. Using RT-qPCR and immunohistochemistry, previous studies have identified some POMC-transcription factors, regulators and processing enzymes to be differentially expressed between FCA and SCA. For example, several G protein-coupled receptor (GPCR) molecules synergistically affect POMC downstream signalling and increase its expression. Also, some GTPases regulating intracellular vesicle trafficking, separately and cooperatively stimulate ACTH secretion in AtT20 cells.

Aim

To investigate differentially expressed genes (DEGs) between FCA and SCA with focus on POMC-expression regulators such as GPCR signalling and intracellular vesicle trafficking and to elucidate the mechanisms behind the SCA silence.

Material and methods

RNA sequencing was performed using Illumina high-throughput sequencing in six FCA (three women, five microadenomas) and six SCA (two women, all macroadenomas). All adenomas stained positive for ACTH. Data were analysed using the tophat 2- cufflinks-CummeRbund pipeline.

Results
We found 631 significant DEGs (fold change (FC) > 1.9, q < 0.05) of which 345 were up-regulated and 286 were down-regulated in SCA compared to FCA. As expected, POMC (FC = 33.3) and POMC transcription factors NUR77 (FC = 6.8) and TBX19 (FC = 3.8) had lower expression in SCA. PCSK2 (FC = 18.3), a POMC processing enzyme, was up-regulated in SCA. Reactome pathway analysis categorized 79 DEGs involved in 'signal transduction' including 12 up-regulated and 16 down-regulated in GPCR signalling. Among these, EDN3 (FC = 190.6), RGS16 (FC = 19.1), GNAS (FC = 2.3), were up-regulated, GNG2 (FC = 3.9), ADCY5 (FC = 5.0), GRK3 (FC = 2.8), MAPK1 (FC = 2.3), and RASGRF2 (FC = 5.9) were down-regulated in FCA compared to SCA. There were 24 DEGs found to be involved in 'vesicle transport'. Among these, RAB8B (FC = 2.7), RAB3C (FC = 2.6) and RAB3GAP1 (FC = 2.4) had lower expression, whereas ALS2CL (FC = 4.1) and TRIP8B (FC = 2.8) had higher expression in FCA compared to SCA.
Conclusion
RNA-seq. analysis showed that the FCA and SCA separate in two groups with a high number of DEGs. Lower POMC- and higher PCSK2 expression in SCA could explain the diminished ACTH production. Interestingly, the opposite regulation of RAB8B and TRIP8B suggests that they have different stimulatory effect on ACTH secretion. Several regulators of GPCR signalling and vesicle transport molecules were found to be differentially expressed and investigating their mechanism of action in further *in vitro* studies will increase our understanding on POMC regulation and may yield valuable knowledge for drug development.

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P784

CGH array analysis of pituitary tumors revealed a highly-disrupted genome

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Introduction
Genetic of pituitary tumors (PT) is incompletely understood. The aim of this study was to search for somatic copy number variations (CNV) in pituitary tumors and evaluate their prognostic impact on tumor recurrence.
Methods
CGH array analysis (Agilent SurePrint G3 Human CGH + SNP Microarray 4× 180 K) was performed on 196 fresh-frozen PT (67 gonadotroph, 31 corticotroph, 38 prolactinomas, 60 somatotroph). PT were classified according to the five-tiered classification grading based on invasion on magnetic resonance imaging, immunocytochemical profile, Ki-67, mitotic index, and p53 positivity. ACGH data were analyzed after centralization, normalization and circular binary segmentation steps. Gains and losses were considered when Log2 ratio > 0.14 and < −0.15 respectively. Hierarchical clustering using Jaccard index was first performed considering altered vs unaltered probes. Effect of quantity of alterations on recurrence was then studied using logistic regression models.
Results
124 patients (63%) presented recurrence during the 5 years of follow-up. Most of PT were macro-adenomas (182) and 84 were invasive PT. Sex ratio males/females was 1.3:1. 84 PT (43%) presented a highly-disrupted genome (>5% of altered probes). Clustering could classify PT according to the tumor type: the cluster of PT with rare alterations gathered gonadotroph tumors together, while the cluster of PT with numerous alterations was heterogeneous and did not separate the prolactinomas from corticotroph and somatotroph PT. Indeed, the quantity of altered probes was higher in prolactinomas (median = 38% of probes, min = 0%, max = 96%) compared to other groups: corticotroph (median = 12%, min = 0%, max = 76%), somatotroph (median = 4%, min = 0%, max = 99%), and gonadotroph which presented rare alterations (median = 0%, min = 0%, max = 22%). Alterations in prolactinomas were preferentially gains (median = 35%, min = 0%, max = 96%) than deletions (median = 0%, min = 0%, max = 24%). When the whole cohort was considered, we were not able to identify a common alteration shared by the different types. We found that the quantity of alterations could not predict recurrence (P value = 0.52) whereas age at diagnosis and clinico-pathological grades could (P value = 0.0006, 0.0003 and 0.00007 for age, grade 2a and 2b respectively).
Conclusions
aCGH analysis of PT showed many CNV which could concern the entire genome in some prolactinomas or somatotroph tumors. The CNV occurrence was highly dependent on tumor type but did not predict recurrence within 5 years of follow-up. PT, except gonadotroph, are characterized by high genomic instability.
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P785

Treatment with antidiabetic biguanide drugs directly impacts the function of multiple pituitary cell types from two non-human primate models

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Antidiabetic biguanides, such as metformin (the most commonly prescribed drug to treat type 2 diabetes) and phenformin, are synthetic insulin-sensitizing agents. In addition to their well-known anti-hyperglycemic actions, biguanides are being also studied in other medical disorders due to the beneficial effects that they exert in important pathologies, including cardiovascular disease or different types of cancer. Although some scattered studies have suggested that metformin could modulate the production of pituitary hormones in certain pathological conditions, there are no previous reports describing the direct role that biguanides may play in the regulation of anterior pituitary cell types in the normal gland, especially in humans or primates. It is widely known that the pituitary gland is a master player in the control of body homeostasis and metabolism, owing to its ability to integrate multiple signals to modulate hormonal secretions that are involved in the control of key peripheral organs/tissues. Accordingly, this study was aimed to elucidate the direct effects of two biguanides (metformin and phenformin) on the expression and secretion of all pituitary hormones in two primate species (*Papio anubis* and *Macaca fascicularis)*, which closely model human physiology. Moreover, to better understand the mechanisms behind the putative actions of these biguanides, we used pharmacological inhibitors of various intracellular signalling-pathways. Metformin and phenformin inhibited basal GH, ACTH and FSH secretion in a dose-and time-dependent fashion, but did not alter PRL, LH or TSH secretion or ghrelin/GHRH-stimulated hormonal release. Moreover, metformin and phenformin also reduced GH and ACTH expression without altering that of other pituitary hormones (PRL/LH/FSH/TSH). Treatment with these biguanides did not affect normal pituitary cell viability. Interestingly, metformin and phenformin increased the expression of sst2, sst5, IGF1R, Ins-R and leptin-R in baboon primary pituitary cell cultures. Finally, we demonstrated that metformin requires PI3K, mTOR and intracellular Ca^{2+} pathways to exert its actions on the modulation of GH/ACTH/FSH secretion, but also MAPK-signalling in the case of GH modulation. Altogether, our results provide strong, primary evidence for the direct actions of biguanides in the control of normal pituitary cell function in two primate models. This information could be relevant for the current understanding of normal human pituitary function in patients treated with metformin, given the likely translation of the findings in primate models into human pathophysiology. Furthermore our results invite to explore potential therapeutic effects of these compounds in pituitary dysfunctions (i.e. somatotropinomas, corticotropinomas and gonadotropinomas).

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P786

Enhanced expression of the transcriptional activators YAP and TAZ in non-secreting pituitary tumours

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The Hippo kinase cascade is a crucial signalling pathway regulating organ growth during development in numerous organs. There is mounting evidence implicating this signalling pathway in tumour formation, where it is emerging as an anti-cancer target due to effective pharmacological inhibition of its transcriptional activators YAP/TAZ. We previously demonstrated activity of the Hippo kinase cascade in the mouse pituitary and nuclear association of YAP/TAZ with SOX2 expressing pituitary stem cells. Here we sought to investigate whether these components are expressed in the human pituitary and if their expression may be deranged in human pituitary tumours. We analysed pathway component expression by immunofluorescence during human pituitary gland development, in the adult pituitary, null cell non-functioning pituitary adenomas (NFPAs), adamantinomatous craniopharyngiomas (ACPs), papillary craniopharyngiomas (PCPs) and prolactinomas. We find that the Hippo pathway is active during human pituitary development and adulthood and that YAP/TAZ are expressed in a similar pattern to SOX2 positive cells. Our data reveal an enrichment of YAP/TAZ in the majority of non-sereting tumours, in contrast to differentiated tumours, which display low or absent levels. To determine the effect of this pathway on endocrine cell type differentiation, we knocked down Lats1, encoding the kinase responsible for phosphorylating and inactivating YAP/TAZ, in the GH3 rat mammosomatotropinoma cells. Loss of LATS1 led to accumulation of both proteins and suppressed *Prl* and *Gh* promoter activity. In conclusion, we have demonstrated activity of the Hippo kinase cascade in the human pituitary and association of YAP/TAZ with the undifferentiated state both *in vitro* in GH3 cells and *in vivo* in the normal pituitary and pituitary tumours. Characterisation of this pathway in pituitary tumours is of potential prognostic value, opening up putative avenues for treatments combating tissue growth.

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P787

Activation of pituitary stem cells through modulation of the LATS/YAP/TAZ cascade

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Pituitary stem cells (PSCs) expressing SOX2 persist throughout life, giving rise to all pituitary endocrine lineages. These cells are highly active at early postnatal stages but this potential declines with age, rendering them mostly inactive in adulthood. The LATS/YAP/TAZ signaling cascade can influence stem cell fate and activity in multiple tissues and we previously identified activity of this axis in the developing and postnatal pituitary. Using a series of genetic manipulations, we aimed to establish the functional role of this axis in PSC regulation in mouse. Conditional deletion of LATS1 kinase in the pituitary is sufficient to lead to accumulation of YAP/TAZ and subsequent anterior pituitary tumour formation. These non-functioning tumours are mostly composed of SOX2 positive cells and display histological features of carcinomas. Genetic experiments targeting only the SOX2 population, identify pituitary stem cells as the cell of origin of the tumours. Conditional expression of a constitutive-active form of YAP in the pituitary does not lead to tumour formation, revealing that YAP alone is not sufficient to mediate this phenotype. However, it is sufficient to drive expansion of the SOX2 pituitary stem cell pool at postnatal stages and to reinstate their activation. Together, out data show a crucial role of the LATS/YAP/TAZ axis in regulation of the pituitary stem cell pool, an important step toward future regenerative approaches.

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Pituitary - Clinical

P788

Sheehan's syndrome: clinical and laboratory evaluation of 80 cases

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Introduction
Sheehan's syndrome (SS) is defined as partial or complete hypopituitarism occurring due to massive postpartum uterine hemorrhage that leads to pituitary infarction. Patients with SS have varying degrees of anterior pituitary hormone deficiency. The aim of our study was to evaluate the clinical and hormonal characteristics of patients with SS.
Methods
Eighteen patients with SS were enrolled in a retrospective and descriptive study. Medical history, physical examination findings and hormonal profiles were documented and analyzed.
Results
The mean age of participants at diagnosis was 41.76 ± 11.31 years, with a mean diagnostic delay of 8.8 ± 8.01 years. Their past obstetric history showed that the mean number of pregnancies was 5.43 ± 2.57, that of deliveries was 4.56 ± 2.41 and miscarriages was 1.24 ± 1.5. Eleven of our patients (13.57%) had a home birth. Seventy-six patients (95%) reported amenorrhea starting immediately after delivery, while four (5%) patients had regular menses after the last delivery. In addition, 67 (83.8%) patients had postpartum agalactia. Overall hormonal assessment at the date of diagnosis revealed that all of the patients had hypogonadotropic hypogonadism and adrenal insufficiency, while 79 (98.8%) patients had secondary hypothyroidism and 72 (90%) patients had prolactin deficiency. Diabetes insipidus has not been found in any patient. Somatropic function was investigated in only 7 patients and was deficient in all of them. Twenty-five patients had pituitary MRI and ten patients had pituitary CT reports. According to CT and MRI findings, 30 patients with SS had a completely empty sella, while five patients had a partially empty sella.
Conclusion
Sheehan's syndrome is a frequent cause of hypopituitarism in underdeveloped countries. Physicians need to be aware of the most important clues for diagnosis to avoid delays in diagnosis and treatment. Appropriate replacement therapy is necessary to reduce the morbidity and mortality of patients.

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P789

Metabolic and cardiovascular outcome in patients with Sheehan's syndrome

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Introduction
Sheehan's syndrome (SS) is postpartum hypopituitarism caused by necrosis of the pituitary gland. Patients with SS have varying degrees of anteriorpituitary hormone deficiency and have an increased mortality from cardiovascular disease. Inadequate hormone replacement is one of the possible causes of this increased mortality. The aim of our study was to assess metabolic and cardiovascular outcome in patients with SS.
Methods
In a retrospective study, we included 80 patients with hypopituitarism due to SS. Metabolic disorders were determined and cardiovascular risk was assessed using Framingham score. 10-year CVD risk was categorized into low risk: $<10\%$, moderate risk: (10–20) and high risk: $>20\%$.
Results
The study population had a mean age of 41.6 ± 11.31 years and a mean follow up period of 23.4 ± 11.2 years. All of the participants had hypogonadotropic hypogonadism and adrenal insufficiency, while 79 (98.8%) patients had secondary hypothyroidism. Somatotropic function was investigated in only seven patients and was deficient in all of them. The mean BMI was $26.55 \pm 5.04\ kg/m^2$. Obesity was found in 15% and overweight in 35% of patients. Prevalences of hypertension, hyperlipidaemia, diabetes mellitus and smoking were 22%, 25%, 21% and 14%, respectively. In all patients, the mean Framingham score was 5.85 ± 5.69. The cardiovascular risk was low, moderate and high in 85%, 11% and 3.7% of patients, respectively. The Framingham score was correlated with age ($r=0.55$, $P<0.001$), fasting plasma glucose ($r=0.42$, $P=0.02$) and systolic blood pressure ($r=0.32$, $P=0.04$).

Conclusion
Patients with SS exhibit a higher cardiovascular risk. The increased cardiovascular morbidity could be attributed to inadequate estrogen or thyroid hormone treatment, also unsubstituted GHdeficiency is probably an important contributing factor.

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P790

Final results of NordiNet® international outcome study: key outcomes

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Background
The NordiNet® International Outcome Study (IOS) (NCT00960128), a non-interventional study (2006–2016), assessed the effectiveness and safety of real-life treatment with Norditropin®. Out of 20,548 enrolled patients, 20,195 (paediatric/adult; 17,711/2484) were included in the full analysis set (FAS) and 12,938 (11,967/971) in the effectiveness analysis set (EAS). Outcomes were assessed in children with growth hormone deficiency (GHD), born small for gestational age (SGA), Turner syndrome (TS), and Noonan syndrome (NS), and in adults with GHD (AGHD).
Methods
Patient information was entered by participating physicians using a web-based system. Among other endpoints, change from baseline in height standard deviation scores (ΔHSDS) and insulin-like growth factor-I (ΔIGF-I) SDS were assessed. Non-serious (NS) adverse reactions (NSARs), SARs, and serious adverse events (SAEs) were recorded. Data are mean (SD).
Results
Patient numbers by indication were (FAS/EAS): GHD, 9967/7141; SGA, 4274/3200; TS, 1374/936; NS, 154/106; AGHD, 2321/971; 'other', 2105/584. At treatment start, patients born SGA (7.9 (3.4) years) were the youngest (GHD, 9.1 (4.1)), TS, 8.7 (3.8), NS, 8.9 (3.8). Average GH dose (mg/kg per day) was lower for GHD (0.032 (0.008)) versus SGA (0.038 (0.009)), TS (0.044 (0.009)) or NS (0.040 (0.009)). Treatment follow-up (years) was longer for patients with TS (4.3 (2.8)) versus GHD (3.8 (2.9)), born SGA (3.6 (2.8)) or NS (3.4 (2.9)). Patients born SGA were shortest (height s.d.s.) at baseline (−2.97 (0.91)) (GHD, −2.55 (1.10), TS, −2.66 (0.93); NS, −2.83 (1.13)). ΔHSDS was greatest in year 1 (baseline to year 1 visit): GHD, 0.69 (0.56); SGA, 0.65 (0.44); TS, 0.54 (0.36); NS 0.51 (0.38). ΔHSDS (baseline to near adult height): GHD, 1.42 (1.19); SGA, 1.11 (0.81); TS, 0.83 (0.87); NS, 1.43 (0.59).
AGHD: age at treatment start (years), females, 46.6 (14.0), males, 49.3 (14.6); mean GH dose (mg/day), females, 0.338 (0.177), males, 0.289 (0.157); treatment follow-up (years), females, 4.9 (4.2), males, 5.0 (4.2) years; baseline IGF-I SDS, females, −1.09 (1.44), males, −1.12 (1.60). IGF-I SDS increased year-on-year from baseline (ΔIGF-I s.d.s. from baseline at year 1: female, 1.20 (1.51), male, 1.52 (1.47)). Safety: no new safety signals were observed. Number of events/number of patients were: paediatric, NSARs, 288/249; SARs, 133/90; SAEs, 352/224; adults, NSARs, 69/54; SARs, 38/29; SAEs, 200/119.
Conclusions
NordiNet IOS data showed that Norditropin was associated with increased HSDS in paediatric patients and increased IGF-I SDS in patients with AGHD supporting the effectiveness of GH therapy. No new safety signals were revealed.

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P791

Relationship between cortisol increment and basal cortisol: implications for the insulin tolerance test in assessing corticotrop insufficiency

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Introduction
The insulin tolerance test (ITT) is accepted as the gold-standard test in the evaluation of adrenal and GH axis in patients with pituitary disorders. Diagnostic criteria that requires a minimum increment in serum cortisol is considered invalid although individuals who have a lower basal serum cortisol concentration because of recent ACTH deficiency may be maximally stimulated by ITT and thus able to further increase cortisol secretion without reaching the cut-off. Analyzing the relationship between cortisol Increment and basal cortisol could lead to precious information, and perform a prediction of adrenal insufficiency (AI). We therefore decided to investigate the relationship between the peak and basal cortisol values after the ITT.
Patients and methods
This was a prospective study in which ITT was performed in 81 patients with pituitary disorders. Serum cortisol was measured. We divided our population in Group 1 (G1): Adrenal Insufficiency (Peak cortisol < 200ng/mL) and Group 2 (G2): normal response (Peak cortisol > 200 ng/ml). Sampling took place at 0, 10, 20, 30, 45, and 60 min. The cortisol increment was plotted against basal cortisol. Receiver-operating characteristic (ROC) analysis was performed to identify a cortisol increment peak with the best sensitivity and specificity for AI prediction.
Results
The mean baseline cortisol levels was 95.40 ± 47.08 ng/ml with a peak level of 179.75 ± 79.005 ng/ml (60^{th} min, $P < 10^{-3}$). In ITT, 44/81 (54.3%) subjects had a peak of cortisol response < 200 ng/ml and were classified as Group 1 (G1). Basal cortisol was significantly lower in the group 1 with 72.68 ± 33.13 ng/ml than in the group 2 with 122.43 ± 47.26 ng/ml ($P < 10^{-3}$). The mean cortisol increment peak in group 1 subjects was 50.61 ± 30.34 ng/ml significantly lower compared to a mean increment peak of 122.02 ± 51.40ng/ml in Group 2 patients ($P < 10^{-3}$). The highest proportion of correctly classified patients (84.04%) evaluated by ROC curve analysis was obtained for ITT-induced cortisol increment peak cut-off of 87 ng/ml (sensitivity 85%; specificity 84%; AUC = 0.885; 95% confidence interval 0.80–0.96).
Conclusion
Our study showed a marked interdependence of the basal cortisol concentration, peak cortisol concentration, and increases in serum cortisol concentration. Our finding indicates that, considering the induced cortisol increment peak cut-off of 87 ng/ml, we can identify, with a statistical concordance, 84.04% of adrenal insufficient under ITT.

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P792

A case of pituitary metastasis in female patient with an invasive breast carcinoma

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Introduction
Pituitary metastases are rare complications of malignancy, representing only 1% of surgical tumours of the pituitary gland. They are usually encountered in elderly patients with disseminated malignant disease. The most frequent are metastases of breast and lung cancer. In this report, we describe a rare case of a metastatic breast cancer to the pituitary gland.
Observation
A 32-year-old female presented with blurred vision and diminished visual acuity in the last two weeks. Her past personal history included invasive ductal breast carcinoma diagnosed 2 years ago, treated with left mastectomy, axillary dissection and adjuvant chemotherapy. In the previous year, multiple bone metastases were diagnosed and she was treated with palliative radiotherapy. The ophthalmic exam displayed a papill edema in both eyes and a bi-temporal hemianopsia. Magnetic resonance imaging of the pituitary region showed a large heterogeneous mass measuring 27 x 22 x 19 mm. Moreover, the mass had a supra-sellar extension and was infiltrating the optic chiasm. Laboratory investigation showed panhypopituitarism. The patient was put on hormone replacement therapy. Then, a transsphenoidal surgery was performed with a subtotal resection of the tumour. The histological findings identified the mass as a malignant neoplasm compatible with metastatic breast cancer and specifically a poorly differentiated adenocarcinoma.
Conclusion
Pituitary metastases are uncommon and difficult to diagnose. Clinical neurological symptoms and signs of panhypopituitarism should suggest the presence of a pituitary metastasis in a cancer patient, particularly in a context of metastatic disease. Diagnosis needs to be confirmed by radiological imaging and histology. Treatment is essentially palliative and depends on the extent of disease and symptoms.

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P793

Non-classical factors of cardiovascular risk in acromegaly

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Background
Acromegaly (ACRO) is associated with greater cardiovascular morbidity and mortality, however, this is not entirely explained by the increase in classic cardiovascular risk factors (CVRF). C-reactive protein, galectin 3, adiponectin, B-type natriuretic peptide (BNP), apolipoprotein E, interleukin-6 and echocardiographic variables such as epicardial fat (EF) and interventricular septum thickness (IST) have been suggested as non-classical CVRF in the general population. Our hypothesis is that these non-classical CVRF could be increased in ACRO and contribute to this higher cardiovascular morbidity and mortality.
Objective
To assess if there are differences in non-classic CVRF in patients with ACRO compared with controls matched by age sex and BMI. Material and methods: We analyzed, 30 patients with ACRO (16 males, 5 with active disease) and 30 matched controls (by age, sex and body mass index (BMI)) with mean age of 53.9 ± 11.0 years. Classic CVRFs, echocardiographic parameters and blood sample with non-classical CVRF determination. were evaluated.
Results
Both cohorts were identical regarding the presence of classical CVRF (hypertension, dyslipidemia, diabetes, and smoking). The ACRO cohort presented higher EF and IST compared to the control group (0.65 ± 0.16 vs. 0.43 ± 0.14 cm, $P = 0.001$ and 11.31 ± 1.17 vs. 10.64 ± 1.47 mm, $P = 0.035$, respectively). Likewise BNP was found higher in the ACRO group compared to controls (32.93 ± 5.50 vs 11.96 ± 2.16 pg / mL $P < 0.0026$. No statistically significant differences were observed in other markers. In the multiple linear regression model that included (ACRO, BNP, gender, adiponectin and IST), only the presence of ACRO and BNP, were independents predictors of EF (ß: 0.34 $P < 0.001$, and ß: 0.05 P: 0.05 and R2Adj. 0.42) influenced by adiponectin that acts as an interaction variable.
Conclusions
Patients with ACRO compared to their paired controls that were homogeneous in classic CVRF, have higher EF and BNP (influenced by adiponectin) EF and BNP have been related to increased cardiovascular complications in the general population and could explain the excess cardiovascular risk in acromegaly.

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P794

A comparison of pituitary function in primary and secondary empty sella: preliminary data

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Background
Empty sella (ES), the herniation of the subarachnoid space within sella associated with a variable flattening of the pituitary gland, is classified as primary (PES) or secondary (SES) on the basis of etiological factors.
Aim
To assess the differences between PES and SES in terms of pituitary function.
Methods
Clinical, radiological and hormonal data were retrospectively extrapolated from the records of 85 patients with a diagnosis of ES made between 1990 and 2016, attending to the Pituitary Unity of Azienda Ospedaliero-Universitaria of Modena, Italy. The pituitary function was assessed by basal hormonal measurements and dynamic tests in an appropriate clinical context. Chi square was used for comparison of categorical variables.
Results
Fifty-nine patients with PES (male/female ratio:1/2) and 26 with SES (male/female ratio:1.4/1) were considered. The mean age at diagnosis was 54 ± 17 years in PES and 45 ± 15 years in SES. Among PES 54% of patients had a normal pituitary function and 64% didn't take replacement treatment, while in SES the percentages decreased to 28% and 35% respectively (Chi-square = 16.8, $P < 0.0001$). Accordingly, the overall number of pituitary deficits was higher in SES than in PES and even each single pituitary deficit occurred more frequently in SES ($P < 0.05$). Mild hyperprolactinemia was present in 24% of PES and 22% of SES. A variable degree of hypopituitarism was found in 36% of PES and 58% of SES. Hypogonadism and growth hormone deficiency were the prevalent deficits among PES (61%) and SES (80%) respectively. The radiological degree of ES (partial vs total) didn't influence the pituitary function.
Discussion
Our preliminary results confirm a higher prevalence of endocrine alterations in SES compared to PES but, in contrast with previous reports in literature, hypogonadism is the most frequent alteration in our PES patients. These data suggest that SES requires a more accurate endocrine screening and follow-up and, if confirmed by prospective studies, may open new insights on the management of ES.

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P795

Thyroid autoimmunity in patients with empty sella syndrome

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Purpose
The aim of this study was to evaluate the association and frequency of thyroid autoimmunity in patients with empty sella syndrome and to evaluate the possible effects of thyroid auto-antibodies on clinical and laboratory findings in patients with empty sella syndrome.
Materials and methods
We recruited 93 patients (female) and 22 male patients (mean age 55.51 ± 14.82) who were admitted to the Endocrinology Clinic of Erzurum Regional Training and Research Hospital between January 2010 and December 2016. 105 healthy individuals (84.8% female) were included in the healthy, body mass index (BMI) normal values and defined as the control group. Empty sella diagnosis was based on pituitary magnetic resonance (MR) results. As a criterion of euthyroid Hashimoto Thyroiditis (HT); Patients with normal thyroid function tests, positive thyroid auto-antibodies and radiologic appearance compatible with HT were accepted as patients.
Results
There was no statistically significant difference between the two groups in terms of BMI, TSH, prolactin, ACTH, GH ($P > 0.05$). Cortisol levels were significantly lower in the patients with empty sella syndrome than in the control group ($P = 0.037$). Empty sella and control groups were evaluated for the association of euthyroid Hashimoto's disease. Euthyroid HT was diagnosed in 41 (35.6%) of the empty sella group and 1 (0.95%) of the control group ($P \leq 0.001$). There was a significant positive correlation between Anti-TPO and Anti-TG and empty sella syndrome ($r = 0.65$, $P \leq 0.001$, $r = 0.63$, $P \leq 0.001$, respectively). There was a statistically significant positive correlation between Anti-TPO and Anti-TG, euthyroid HT, age, BMI, right thyroid volume, left thyroid volume, FT3 and FT4 ($P < 0.05$). In ROC analysis, sensitivity for Anti-TPO ≥ 9.5 was 94.5% and specificity 72% for empty sella. For Anti-TG $\geq$ 10.5, the sensitivity was 80% and the specificity was 79%. The AUC value of Anti-TPO was 87.9% ($P \leq 0.001$) and the AUC value of Anti-TG was 86.4% ($P \leq 0.001$).
Discussion
There is a positive relationship between thyroid auto-antibodies and the clinical and laboratory findings of the empty sella. As a result, it is possible that some of the idiopathic empty sella syndrome cases occur via HT. It is advisable to investigate the presence of HT in patients with empty sella syndrome. Therefore, when supported by controlled clinical trials, it will be clear that future euthyroid HT may be a risk factor for empty sella. Further work is needed.

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P796

Assessment of prevalence and severity of depressive symptoms in patients with acromegaly using the beck depression inventory II (BDI-II) – own observations

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Background
Prolonged exposure to excessive concentrations of GH and IGF-1 in acromegaly continues to affect patients' appearance and negatively influences their self-evaluation, personal relations and morbidity. Besides chronic GH/IGF-1 excess could be deleterious to the brain through many mechanisms.
Objectives
The aim of the study was to evaluate the influence of acromegaly on the prevalence and the severity of depressive symptoms in patients with cured or controlled and uncontrolled disease in own material.
Material and methods
The study group comprised 56 patients with acromegaly. On the basis of GH and IGF-1 levels the whole group was divided into two subgroups: with controlled/cured and with uncontrolled acromegaly. The presence and severity of depression were assessed on the basis of Beck Depression Inventory II.
Results
The mean score of BDI-II was 13.43 ± 10.41. There was no significant difference in the severity of depressive symptoms between patients with cured/controlled and uncontrolled acromegaly ($P = 0.620$), with micro and macroadenomas or with and without hypopituitarism. There were no significant correlations between BDI-II scores and GH or IGF-1 levels, patients' age or duration of the illness.
Conclusions
In acromegalic patients depression rates are higher than in healthy people, even if remission had been attained. This indicates the need for an early diagnosis, before the development of advanced complications and significant changes in patients' appearance. In order to optimize the management, dimensions that reflect mental state and quality of life should be evaluated. In some cases providing emotional support to the patients could be very helpful or even necessary.

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P797

Giant prolactinomas in men: clinical features and therapeutic outcomes

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Aims
To evaluate the clinical features and long-term therapeutic outcome of giant prolactinoma (gPRLoma) in men and to compare them with those of a group of male patients with non-gPRL macroprolactinomas (non-gPRLomas).
Patients and methods
A retrospective and multicenter study of gPRLomas in men diagnosed in a 20-year period was performed. Clinical data and treatment outcome were registered. The diagnosis of gPRLoma was established when the maximal tumor diameter was $\geq$ 40 mm or the tumor had $\geq$20 mm of suprasellar extension associated to hyperprolactinemia (PRL > 1000 ng/ml). Non-gPRLoma was considered when tumor diameter was $\geq$ 10 mm and $<$40 mm associated to hyperprolactinemia (PRL $\geq$ 200 ng/ml).
Results
Twenty three patients with gPRLoma (age 38.3 ± 13.5 yr) followed for at least 3 mo were evaluated. A group of 42 patients with non-gPRLoma served as a control group. More than half (56.5%) of the gPRLoma patients were younger than 40 years at diagnosis. Visual disturbances were significantly more common in gPRLoma than in non-gPRLoma patients (65.2 vs 25.6%; $P = 0.004$). Prevalence of hypopituitarism was similar in both groups of patients (73.9% vs 80.9%; gPRLoma vs non-gPRLoma; NS). Serum PRL concentrations were significantly higher in gPRLoma than in non-gPRLoma patients [median (IR), 3978 ng/ml (1179-9012) vs 907 ng/ml (428-3119); $P < 0.001$]. Maximum tumor diameter in gPRLomas was 4.8 ± 0.8 cm and 2.4 ± 0.7 cm in non-gPRLoma ($P < 0.001$). All patients were treated with dopamine agonists (DA). Surgery was used in 12 (52.2%) gPRLoma patients and in 12 (28.6%) non-gPRLoma patients ($P = 0.054$). Lastly, radiotherapy was used in 5 (21.7%) gPRLoma patients and in 6 (14.2%) non-gPRLoma patients (NS). At last visit, PRL was similar in both groups of patients and tumor size decreased significantly ($P < 0.001$) in both groups of patients. Clinical cure (maintained normoprolactinemia without therapy for $>$ 1 yr and no radiological evidence of pituitary tumor) was achieved in 2 (8.7%) gPRLoma patients and in 2 (4.8%) non-gPRLoma patients (NS).
Conclusion
gPRLomas in men are usually diagnosed at the age of 40 yr, an age similar to that of non-gPRLomas. The only clinical difference with non-gPRLomas is their greater prevalence of visual disturbances. The therapeutic approaches and tumor outcomes were similar to those obtained in patients with non-gPRLomas. Complete cure in gPRLoma is rare, but similar to that achieved in non-gPRLomas, reaching in less than 10% of patients.

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P798

Static and dynamic balances in acromegaly and impact of exercise on balance

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Purpose
Patients with acromegaly may have changes in balance due to visual disturbances, musculoskeletal abnormalities and changes in body composition. We aim to compare static and dynamic balances in patients with acromegaly and healthy controls and to evaluate effects of exercise on balance in patients with acromegaly.
Methods
Twenty-two patients with acromegaly followed at the Endocrinology Outpatient Clinic of Istanbul University, Cerrahpasa Medical Faculty and 11 healthy volunteers were included in the study. The participants (all right-handed) who had vestibular or neurological diseases or physical disabilities were not enrolled in the study. The patients with acromegaly were divided into 2 groups. Eleven patients with acromegaly (group A) were attended to an exercise program which included 75 minutes exercise session, 3 days a week for 3 months whereas the remaining 11 patients with acromegaly (group B) and healthy volunteers (Group C) didn't take any exercise. Bipedal and unipedal stance static and dynamic balance tests were performed using Prokin 5.0 device.
Results
The ages, gender distribution and educational status were similar between groups. The disease remission status of Group A and B were also similar. The body mass indices of all patients with acromegaly were higher than the control group ($P = 0.017$). When all patients with acromegaly were compared with healthy controls; bipedal static balance values were similar but in unipedal stance analysis, displacement of center of pressure in anterior-posterior direction (C.o.P.Y) was seen in patients with acromegaly when left leg was used when compared with healthy controls ($P = 0.019$). In addition, dynamic balance measurements at forward-backward sway to the left direction were also different than normal ($P = 0.027$). When the exercise effect on balance were evaluated between Group A and group B; the eyes-open pre and post exercise bipedal stance values of patients were similar whereas post-exercise eyes-closed bipedal stance C.o.P.Y ($P = 0.01$) and right and left leg unipedal stance values ($P = 0.02$ vs $P = 0.03$) got better after exercise in Group A. Additionally, various parameters of dynamic balance measurements of both forward-backward and right-left sway also got better after exercise ($P = 0.01$ and $P = 0.006$ respectively).
Conclusions
Imbalances on unipedal stance static and dynamic measurements on left direction were detected in patients with acromegaly, when compared with healthy controls. In addition, eyes-closed anterior-posterior displacements, imbalances on unipedal stances and impairments on dynamic balances on both forward-backward and right-left sway got better with exercise.

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P799

Severe hypernatremia resulting in a locked-in syndrome

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Introduction
Osmotic demyelination syndrome (ODS) is a well described, potentially devastating consequence of rapid alterations in plasma osmolality, classically occurring secondary to the excessively rapid correction of chronic hyponatraemia. We describe a case of diabetes insipidus (DI) resulting in a Locked-in syndrome (LIS) caused by a rapidly developing severe hypernatremia.
Case report
A 43-year-old woman was admitted to the Internal Medicine ward with a clinical diagnosis of urinary tract infection. Her past medical history included panhypopituitarism, DI without adipsia and multiple meningiomas secondary to craniopharyngioma treated with surgery and radiotherapy during childhood, without difficulties to control sodium level. On admission, sodium level was within the normal range (138 mEq/L (135-145)). Three days later her level of consciousness was diminished. Lumbar puncture and electroencephalogram excluded both encephalitis and non-convulsive status epilepticus. Blood examination revealed high sodium level (180 mEq/L). The patient was aggressively fluid resuscitated with normal saline and was administered intravenous desmopressin. With 24, 48 and 72 hours, serum sodium decreased to 168, 159 and 151 mEq/L respectively. But despite achieving normal sodium levels, her neurological condition didn't improve. She could open her eyes spontaneously, but she couldn't speak or follow orders, and she was otherwise quadriplegic, so a suspicion of a LIS was raised. A brain MRI showing hyperintense lesions in the brainstem confirmed the ODS as the cause for the LIS.
Conclusions
Although reports of severe hypernatremia resulting in a ODS are few, rapid alterations in plasma osmolality – rather than only the correction of hyponatremia – are real cause for it. Physicians involved in the management of patients with difficulty control of plasma osmolality should be extremely cautious with rapid changes, as the consequences can be devastating.

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P800

Thyroid autoimmunity and euthyroid hashimoto thyroiditis frequancy in patients with pituitary adenoma

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Purpose
The purpose of this study were to evaluate the relation thyroid autoimmunity and euthyroid hashimoto thyroiditis in patients diagnosed with pituitary adenoma and association of pituitary adenoma with clinical and laboratory findings
Materials and methods
The retrospective study population included a total of 230 participants. A total of 189 patients (67 with prolactinoma, 35 with acromegaly, 4 with cushing disease and 83 with non-functional pituitary adenoma) were included this study; 41 healthy subjects with similar age and sex and without pituitary adenoma in pituitary MR were used as the control group. This study was conducted at the Erzurum Regional Training and Research Hospital Endocrinology Medicine Clinic and all participants were tested for thyroid autoantibodies.
Results
Body mass index (BMI) ($P=0.005$, $p\leq0.001$, $P=0.027$, respectively),waist circumference (WC) ($P=0.001$, $P\leq0.001$, $P\leq0.001$, respectively), fasting blood glucose (FBG) values ($P=0.04$, $P=0.048$, $P=0.015$, respectively) of the patients with acromegaly were higher and HDL values ($P=0.035$, $P=0.012$, $P=0.007$, respectively) were lower than those of the control, non-functional pituitary adenoma and prolactinoma group. LDL values of the all patients with pituitary adenoma are significantly increased in cases than controls($P\leq0.05$). Anti-TG ($P=0.011$) and Anti-TPO ($P\leq0.001$) values were significantly higher in patients with pituitary adenoma compared to healthy subjects values. Anti-TPO and Anti-TG positivity was detected 7.3%, 4.9% in control group, 18.1%, 19.3% in patients with non-functional adenoma, 13.4%, 16.4% in prolactinoma group and 14.3%, 22.9% in acromegaly group. Anti-TG 18.5% positive and anti-TPO 15.9% positive were detected in all patients with pituitary adenoma. The frequency of euthyroid HT was significantly higher in the patients with acromegaly (22.9%), prolactinoma (14.9%) and non-functional adenoma patients (19.3%) than the control group ($P=0.006$, $P=0.037$ and $P=0.01$, respectively). Correlation analysis reveals significantly positive correlation of Anti-TPO ($r=0.210$; $P=0.001$) and Anti-Tg ($r=0.338$; $P\leq0.001$) with pituitary adenoma. The ROC showed that Anti-TPO (AUC = 0.66) with sensitivity (58%) and specificity (79.9%) and Anti-Tg (AUC = 0.76) with sensitivity (74%) and specificity (74.6%) levels could be used as markers to diagnose pituitary adenoma ($P=0.001$ and $P\leq0.001$).
Conclusion
Comparing the control group with pituitary adenoma, it was seen that the thyroid autoantibodies were significantly higher in the patient group. In our study, we found a strong association between euthyroid HT and pituitary adenoma and we think that thyroid autoantibodies may play a role in the etiopathogenesis of pituitary adenoma. We think that further, wide-ranging studies are needed.

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P801

Gonadotroph pituitary macroadenoma inducing ovarian hyperstimulation syndrome

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Case report
We report a young woman with ovarian hyper stimulation syndrome (OHSS), headache, visual field defect and pituitary macro adenoma. The patient was treated about four years ago as pituitary PRL-secreting adenoma with carbergoline. The evaluation of other hormones FSH, LH and Estradiol values wasn't done. The patient presented to our hospital with abdominal pain and headaches and amenohrrea. The pregnancy test was negative and pelcic ultrasound demonstrated enlarged ovaries with multiple cysts. The case was treated with GnRH agonist by gynecologist, but and the ovaries remain hyper stimulated and the estradiol and FSH values very high. The biopsy of ovaries was negative for malignancy (follicular luteinisation cysts. The pituitary macro adenoma secreting FSH was suspected. The laboratory results: β-HCG negative; Prolactine 83 ng/ml (N 4.3-32.3 ng/ml), FSH 103.3 IU/l (N 6.3-22 IU/l), LH 1.9 (N 1.5-8 IU/l), Estradiol > 3000 pg/ml (N 38-200). The other hormones normal. MRI of the pituitary gland: Pituitary macroadenoma $35\times20\times25$ mm with suprasellar extension, elevation and compression of the optic chiasm. Immunohistochemical staining of the pituitary adenoma specimen was positive for α subunit, FSHβ subunit and LHβ subunit; staining was negative for growth hormone, prolactin, adreno-corticotropic hormone and for TSH. The patient was diagnosed with gonodotrope cell adenoma with secondary ovarian hyperstimulation. After surgery of pituitary gland the gonadotropin and estradiol levels returned to normal range. Menstrual cycles resume and the ovaries revert to normal size with cyst remission.
Conclusion
Surgical resection is the definitive and primary therapy for OHSS due to gonadotropin-secreting adenomas. In those with recurrent tumors, radiation therapy may be required. In a patient with abdominal pain, irregular menses and multicystic ovaries the clinicians should measure the estradiol and gonadotropin levels to exclude OHSS.

Keywords: gonadotrope adenoma, ovarian hyperstimulation syndrome
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P802

Associated pituitary insufficiencies in children with growth hormone deficiency

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Context
GH deficiencies could be associated with other pituitary insufficiencies. Our main objective is to assess othe pituitary secretion in short stature patients.
Patients and methods
Twenty three patients (17 boys, 6 girls) were included in the study for exploration of short stature, after oral and informed consent of their parents, from January 2016 to June 2017 in the Department of Endocrinology of the University Hospital of Farhat Hached Sousse. The mean age of the patients was 11.30 ± 2.83 years. Patients were excluded if they had a known chromosomal abnormality, untreated primary hypothyroidism, metabolic disease or disease associated with disordered glucose metabolism, MRI abnormalities, a known endocrine abnormality that could interfere with HPA axis function, were treated by any kind of steroid preparation, or had an anatomic abnormality or tumor of the central nervous system, a history of central nervous system irradiation, or documented central or primary hypothyroidism. The Inslin Tolerance Test (ITT) was performed by administering an IV bolus injection of 0.10 U/kg regular human insulin (Actrapid*). The Glucagon Stimulation Test (GST) was performed by intramuscular injection of 1 mg glucagon. We assessed the other pituitary axis by hormonal assays: TSH and T4 for the thyroid deficiency, ACTH and cortisol for adrenal insufficiency and Gonadotrophins for gonadic axis.
Results
From 23 children with short stature, 15 had GH deficiency (GHD) confirmed by both of Insulin tolerance test and Glucagon stimulation test. The mean age of the patients was 10.67 ± 3.24 yo. The mean height was 164.33 ± 4.22 cm, with a standard derivation (SD) of -2 DS for 53.3% and -3 DS for 46.7%. Hypophysary MRI performed in 6 children was normal. The bone age was of 10.13 ± 2.85 yo. They were 12 boys and 3 girls. The mean peak of GH under ITT and GST was respectively of 1.95 ± 1.04 ng/ml and 2.92 ± 1.7 ng/ml significantly lower than normal children ($P < 10^{-3}$). Of the children with GHD, 5 of them had secondary adrenal insufficiency confirmed by both of ITT and GST, 3 of them had hypogonadotropic hypogonadism and 1 of them had central hypothyroidism. None of them had hyperprolactinemia.
Conclusion
GH deficiency could be associated with other pituitary insufficiencies that may be asymptomatic in children with short stature. Assessing the entire pituitary secretion may discover these deficiencies and permit earlier treatment.

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P803

Metastasis – A rare cause of diabetes insipidus and pituitary insufficiency

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Introduction
Metastases in the pituitary gland are an uncommon presentation of carcinomas, lung and breast being the most common sites of the primary tumor. The most frequent clinical manifestations are diabetes insipidus, visual disturbances, cranial nerve paralysis and hypopituitarism.
Case report
We report the case of a 64 years old man, smoker, with no chronic illness, with one year history of headache, and more recent asthenia, weight loss, poliuria, polidipsia, loss of appetite. The MRI exam revealed a 20/14/12 mm sellar tumoral mass that interest the pituitary stalk. The endocrinological assessment confirmed diabetes insipidus, hypopituitarism and hiperprolactinemia (TSH = 0.5 uUI/ml, n.v = 0.4–4, FT4 = 0.6 ng/dl, n.v = 0.89–1.76; FSH = 0.32 U/l, n.v = 0.7–11.5, LH = 0.1 U/l, n.v. = 0.8–7.6; testosterone < 0.1 ng/ml, n.v = 1.3–8.53; cortisol = 4.46 mcg/dl, n.v = 5–25; PRL = 76.1 ng/ml, n.v = 2.5–17). He started treatment with Prednison 5 mg/day, Desmopresin 120 mcg/ twice daily, then Euthyrox 50 mcg/day and then he underwent surgery. The histological exam revealed a metastatic lesion of a poorly differentiated lung adenocarcinoma. The chest CT scan confirmed multiple pulmonary lesions and mediastinal lymph node metastasis. No secondary lesions on abdominal CT scan. The postoperatory hormonal assessment reconfirmed hypopituitarism, hyperprolactinemia and diabetes insipidus (STH = 2.09 ng/ml, n.v = 0–7; TSH = 0.5 uUI/ml, n.v = 0.4–4, FT4 = 0.98 ng/dl, n.v = 0.89–1.76; FSH = 0.28 U/l, n.v = 0.7–11.5, LH = 0.1 U/l, n.v. = 0.8–7.6; testosterone < 0.1 ng/ml, n.v = 1.3–8.53; cortisol = 1.47 mcg/dl, n.v = 4–25; PRL = 47.9 ng/ml, n.v = 2.5–17). He continued the same substitution therapy and he also underwent cranial radiotherapy.
Conclusion
Diabetus insipidus and pituitary insufficiency may be the first and only manifestation of malignancy. The detection and appropriate treatment of hormonal insufficiency are important to improve the quality of life.

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P804

Endocrine abnormalities in primary empty sella syndrome

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Background
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 our study was to evaluate hormonal abnormalities associated with PES.
Methods
Thirty-six patients with PES were retrospectively analysed over a 24-year period [1992-2016].Patients were evaluated for pituitary function with basal hormone levels (FT4, TSH, GH, IGF1, FSH, LH, cortisol,ACTH, prolactin) and dynamic testing when necessary.
Results
Our study included 26 women and 10 men with PES. The revealing symptoms were dominated by endocrine signs (52.7%). At least one pituitary hormone deficiency was found in 72% of cases. Secondary adrenal insufficiency was the most common hormonal abnormality (42.85%) followed by hypogonadotropic hypogonadism (34.2%). Central hypothyroidism,mild hyperprolactinemia and central diabetes insipidus were also recorded in 19.4%,19.4% and 5.5% of patients,respectively. Somatotrophic axis was not adequately assessed. The percentage of hypopituitarism in complete PES was significantly higher than that in partial PES ($P < 0.05$).
Conclusion
Our study showed that endocrine alterations are frequent in patients with PES syndrome and that the association of central diabetes insipidus with PES isn't a very rare event.Moreover, a correlation was found between the residual pituitary gland and the degree of pituitary dysfunction. Thus, a prompt evaluation and an early hormone replacement therapy are always recommended for better quality-of-life.

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P805

Long-term outcomes of different treatments for cushing disease: a retrospective study

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Introduction
Cushing disease (CD) results from excessive exposure to glucocorticoids caused by an adrenocorticotropic hormone–secreting pituitary tumor. Inadequately treated CD is associated with significant morbidity and elevated mortality.
Objetive
The study purpose was to describe the long term treatment outcomes for CD patients in our hospital.
Methods
Retrospective analysis of the records of 36 patients with Cushing disease with more than 5 years of follow up. Descriptive statistical analyses were conducted to examine presenting signs, laboratory data and treatment outcomes.

Results
75% were female, median age at diagnosis 39.7 years (range:12–72 years). Pituitary adenomas size were 3–20 mm, 69.6% microadenomas, 21.7% macroadenomas. Blood test: Mean ACTH 68.04 pg/ml(normal range 5–52 pg/ml), 50% > 52 and 50% < 52 pg/ml. 85.7% had positive dexametasone 1 mg supresión test, 71.4% positive 8 mg supression test, 86.4% elevated UFC, 66.7% elevated salival nocturnal cortisol. 15% of patients had 3 positive test, 65% 2 positive test. Inferior petrosal sinus sampling (IPSS) were needed in 34.2%. First line Treatment: 100% underwent TSS (transesphenoidal surgery). The remission, recurrence and persistence rate were: 36.4%, 36.4% and 27.3% respectively. Remision rate after "normal anatomopathology" was 57.1%. Remission rates: in patients <30 years old remision rate was 12.5% vs >30 years 50%, micro 41.7% vs macro 33.3%,women 43.8% vs men 16.7%, early postsurgery cortisol < 10 μg/dL 100% vs cortisol >10 μg/dL 12.5%. Mean time between first treatment and first recidive: 6.7 years. Non cured patients in first line treatment: Mean time between second treatment and second recidive: 11.5 years. 70% had "normal conventional RM" and were diagnosed with ·3T RM/metionin PET, 69.2% underwent second TSS and 30.8% radiotheraphy. Remission, recurrence and persistence rate after second line treatment were: 50%, 7.1% and 42.9% respectively. After all treatments 68.2% are cured (13.3% with panhipopytuitarism)and 31.8% are non cured, with ketokonazol and waiting for definitive treatment).
Conclusion
Despite multiple treatments, at the end of follow-up, remission was still not achieved in 31.8% of patients. Early possurgery cortisol is the best predictor of remission after surgery.

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P806

Association between prolactin level and tumor size reduction at 3 months after cabergoline treatment in patients with macroprolactinoma

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Objectives
Prolactin (PRL) normalization after 3 months of Cabergoline (CAB) treatment are useful predictors of responsiveness in patients with prolactinoma. However, differences within the PRL normalization cut-off value have not been identified.
Methods
We reviewed the medical records of patients with prolactinomas who were treated with CAB as a primary drug at Severance Hospital. We included patients who had a full dataset of pituitary hormone assays and sella MRI at baseline, follow-up PRL assay and sella MRI at 3 months after CAB treatment.
Results
Among the 217 patients, 123 patients had macroprolactinoma. After 3 months of CAB treatment, PRL normalization was achieved in 109 (88.6%) of macroprolactinoma patients, the mean size reduction was 22.9%. We divided these patients into two groups according to the PRL level at 3 months. When we classified by 5 ng/ml, low normal group ($PRL \leq 5$, $n=82$) and high normal group ($5 < PRL \leq 20$, $n=27$) did not differ in baseline PRL, tumor size and size reduction. When we classified by 1 ng/ml, low normal group ($PRL \leq 1$, $n=49$) and high normal group ($1 < PRL \leq 20$, $n=60$) did not differ in baseline PRL and tumor size. However, size reduction was significantly different between the two groups (27.18 ± 18.31 vs. $19.46 \pm 13.87\%$, $P=0.014$). Even if we narrow down the high normal group ($1 < PRL \leq 10$, $n=50$ and $1 < PRL \leq 5$, $n=33$), similar results came back (27.18 ± 18.31 vs. $19.30 \pm 13.66\%$, $P=0.017$ and 27.18 ± 18.31 vs. $19.22 \pm 14.33\%$, $P=0.039$).
Conclusion
Prolactin drops to less than 1 ng/ml at 3 months after CAB treatment predicts better response of macroprolactinoma.

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P807

Predictors of clinical behavior of pituitary adenomas

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The aim of this study was to investigate the expression of histological markers Ki-67, p53 and mitotic activity in pituitary adenomas and their correlation with the frequency of recurrence and progression of residual adenoma. The study comprised 94 patients treated at the Department of Endocrinology, University Hospital Center Zagreb in the period from 2005 to 2011. After the operation, 63.8% of patients had residual adenoma. In the minority of patients (12/60 patients, 20%) with residual adenoma we detected increase in size. In patients with complete adenoma resection, only few patienst had recurrence (3/34 patients, 8.8%). The size of the denoma had a significant prognostic value for residual tumor ($P=0.027$). In majority of adenoma samples (74.5%) expression of Ki-67 was less than 3%, 26.1% had positive p53 while only 9.6% had mitotic activity. Functional adenomas had significantly higher expression of Ki-67 compared to nonfunctional adenomas ($P=0.012$). The expression of the Ki-67 in the pituitary adenoma correlated positively with the recurrence of adenoma as well as the increase in residual adenoma ($P<0.001$). Cut-off value of Ki-67 $\geq 3\%$ was significant for the time of residual adenoma progression or adenoma recurrence after complete removal ($P=0.007$). All patients with residual adenoma, regardless of the clinical outcome, had a significantly higher expression of Ki-67 compared to patients without residue ($P=0.009$). Patients with residual adenomas had significantly larger and more invasive adenomas ($P<0.001$ and $P=0.002$, respectively). In patients with enlargement of residual adenoma or recurrence after complete removal, the expression of Ki-67 was higher compared to patients with stable residue or complete adenoma removal ($P<0.001$). Patients with increased residue size and recurrent adenomas had significantly larger initial size of the adenoma ($P=0.045$). Moreover, these patients had higher expression of Ki-67 compared only to the group of patients with stable residue ($P=0.005$). Based on this study we can conclude that patients with larger adenoma size and higher expression of proliferative marker Ki-67 have an increased chance of progression of residual adenoma or recurrence after complete removal.

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P808

The comparison of combination test either with 1 μg acth test and glucagon test for the evaluation of hypothalamo-pituitary-adrenal axis in patients with pituitary disorders

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The low-dose (1 μg) ACTH stimulation test or glucagon stimulation test (GST) are candidate tests for hypothalamo-pituitary-adrenal (HPA) axis evaluation in patients with pituitary disorders. In this study, we aimed to compare the combination of low-dose ACTH and GSTs (named as combination test) with each test results alone in the evaluation of HPA axis in patients with pituitary disorders whether combination test may overcome the problems when the test results are equivocal.
Patients and methods
Forty-one adult patients with pituitary disorders and 20 healthy subjects were included in the study. Patients with diabetes mellitus or with the diagnosis of Cushing's syndrome were not included in the study. Low-dose ACTH test, GST and combination tests were performed on separate days. Blood samples for the measurement of cortisol were obtained in the basal state and at 30, 60, 90 and 120 min after the administration of 1 μg ACTH intravenously. The lowest peak cortisol value of control subjects (14.6 μg/dl) was considered as the cut-off value for adrenal insufficiency in low-dose ACTH test. The GST was performed by subcutaneous injection of 1 mg glucagon. Blood samples for measurement of cortisol were obtained at 90, 120, 150, 180, 210 and 240 min after glucagon injection. The lowest peak cortisol value of control cubjects (9.7 μg/dl) was considered as the cut-off value for adrenal insufficiency. Combination test was performed by injecting 1 μg of ACTH at the 180 min of GST and blood samples

for cortisol measurement were obtained at 210 and 240 minutes. For the determination of optimal cut-off value for diagnosing adrenal insufficiency, Receiver Operating Characteristics (ROC) analysis was performed and 12.4 μg/dl of cortisol value was obtained with a sensitivity of 83% and specificity of 100%.
Results
Ten patients with adrenal insufficiency in both tests also had adrenal insufficiency in the combination test. Twenty-eight patients with normal cortisol response to both tests also had normal cortisol response to combination test. Two patients with adrenal insufficiency (peak cortisol responses were 13.4 and 13.1 μg/dl) at ACTH test and a patient with adrenal insufficiency at GST (peak cortisol response 8.7 μg/dl) had normal cortisol responses to combination test.
Conclusion
The combination test gave an additional information in three (7.3%) patients who had equivocal results in ACTH and glucagon tests. Moreover, by performing the combination test, we can save a day of the patients and evaluate GH axis concomitantly.

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P809

Clinical parameters to distinguish silent corticotroph adenomas from other non-functioning pituitary adenomas

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Silent corticotroph adenomas (SCAs) are difficult to distinguish from other non-functioning pituitary adenomas (NFPAs) preoperatively. This study assessed the preoperative clinical parameters associated with SCAs. After excluding patients with increased 24-h urinary free cortisol, 341 patients who underwent surgery for NFPAs during 2011–2016 with available preoperative combined pituitary function test (CPFT) and immunohistochemical staining results were enrolled. The patients' medical records were retrospectively reviewed. The age and tumour size were similar between patients with SCAs and other NFPAs. The percentages of female patients (89.2 vs. 57.6%, $P<0.001$), cavernous sinus invasion (35.1 vs. 20.7%, $P=0.047$), and intra-tumoural haemorrhage on preoperative sella magnetic resonance imaging (32.4 vs. 9.2%, $P<0.001$) were higher in the SCA group. In the preoperative CPFT, the peak adrenocorticotropic hormone (ACTH) (67.80 ± 49.83 vs. 85.67 ± 78.97 pg/mL, $P=0.061$) tended to be lower, and the ΔACTH (53.71 ± 50.14 vs. 72.67 ± 75.82 pg/mL, $P=0.046$) was significantly lower in SCAs. After excluding patients with preoperative hypopituitarism caused by mass effects, the peak ACTH (69.39 ± 39.45 vs. 119.75 ± 89.84 pg/mL, $P=0.001$) and ΔACTH (58.58 ± 36.51 vs. 107.66 ± 86.05 pg/mL, $P=0.001$) were significantly lower in SCAs. Female sex, cavernous sinus invasion, intra-tumoural haemorrhage on sella magnetic resonance imaging, and decreased ACTH response are independent indicators of SCAs.

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P810

Male hypogonadism – when two endocrine causes merge in the same patient

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Introduction
Male hypogonadism is defined by lower levels of testosterone than expected for age-matched individuals. In primary or hypergonadotropic hypogonadism, LH and FSH show a compensatory elevation to low testosterone levels, while in the secondary or hypogonadotropic hypogonadism the low testosterone levels are a result of insufficient gonadotropin levels. Hyperprolactinemia is a cause of hypogonadotropic hypogonadism. It is not only caused by lactotroph adenomas (prolactinomas), but may also develop due to pharmacological or pathological interruption of hypothalamic-pituitary dopaminergic pathways, sometimes also idiopathic. Klinefelter syndrome is a common sex-chromosome aneuploidy with clinical features that include the development of hypergonadotropic hypogonadism.
Clinical case
Case of an asymptomatic 57-year-old male patient referred to a Endocrinology department after the incidental diagnosis of a pituitary macroadenoma in a tomography of the paranasal sinus (pituitary mass with $23\times15\times13$ mm). He had no offspring. His medical history included heart failure secondary to idiopathic dilated cardiomyopathy, essential hypertension and chronic atrial fibrillation, medicated with furosemide 40 mg id, isosorbide mononitrate 5 mg id, captopril 50 mg id, spironolactone 25 mgid and warfarin. Clinical examination revealed a mild gynecomastia, a BMI of 32 and a 179 cm height. The initial lab results included prolactin level of 1155 ng/ml (4–15 ng/ml), FSH 8.5 U/L (1.5–12.9 U/l), LH 6.83 U/l (1.3–9.8 U/l) and a total testosterone of 241.1 ng/dl (190–740 ng/dl). He was started on bromocriptine 20 mg/day and, after 6 months, prolactin levels had lowered to 527.5 ng/ml, with increasing of FSH (13.7 U/L) and LH (8.47 U/l) and a total testosterone of 95 ng/dl. 3 Years later, bromocriptine was switched to cabergoline 1 mg/per week, with a sustained lab response (prolactin 107 ng/dl, 6 months after the switch) and tumor size reduction (absence of supra-selar extention in a CT 1 year after the switch). Despite the good responsiveness of prolactin levels to dopamine agonists therapy, testosterone levels remained low (88.1 ng/dl) with increased gonadotropins (FSH 26.3 U/l and LH 12.8 U/l). A karyotype was requested, and after the result of 47, XXY, the diagnosis of a Klinefelter syndrome was established.
Conclusion
The underlying hypergonadotropic hypogonadism was initially masked as a result of gonadotropin suppression by high levels of prolactin. The reduction of prolactin levels was accompanied by a paradoxical decrease of testosterone and increase of gonadotropin levels raising the clinical suspicion of a preexisting Klinefelter syndrome. The diagnosis of Klinefelter syndrome is important to alert the clinician to other common comorbidities.

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P811

The diagnostic utility of late night salivary cortisol (LNSF) and cortisone (LNSE) in Cushing's Syndrome and their relationship to metabolic markers

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The diagnosis of Cushing's Syndrome (CS) requires demonstration of excess circulating cortisol. Measurement of late night salivary cortisol (LNSF) has been advocated as a simple, non-invasive and reliable outpatient diagnostic tool for patients with suspected CS but the usefulness of its metabolite cortisone (LNSE) remains unclear. LNSE levels are approximately six times higher than LNSF in saliva due to the rapid action of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD), and have been shown to have a linear relationship with serum free cortisol. We hypothesised that LNSE concentrations may therefore correlate with degree of metabolic derangement resulting from hypercortisolemia. In this study, we investigated the sensitivity of LNSF and LNSE (measured using liquid chromatography-mass spectrometry, LCMS) as compared to the traditional urine free cortisol (UFC) and overnight dexamethasone suppression test (ONDST) in patients with confirmed CS. We also studied any association between LNSF or LNSE and metabolic parameters affected by cortisol excess including HbA1C, ALT and blood pressure (BP). Eighteen patients (15 female) with confirmed CS attending Beaumont Hospital were included. Sixteen patients had ACTH-dependent CS. Median age was 34 years (range 7 – 65). Both LNSF and LNSE were strongly correlated with UFC (R 0.53, $P=0.03$ and R 0.69, $P=0.01$ respectively). Sensitivity of ONDST was 100% (data for 17 patients). UFC was measured in 17 patients – median number of samples 1.5 (range1–6) with a sensitivity of 92%. One patient with confirmed CS had four measurements for UFC, all of which were negative. Median number of LNSF and LNSE samples measured was 3 (range 1–18). LNSF had a sensitivity of 91%, while LNSE had a sensitivity of 84%. Seventeen of 18 LNSF samples were positive in the patient with four negative UFCs. Serial LNSF and LNSE identified four patients with cyclical Cushing's Disease. Six patients (33%) had diabetes mellitus, 11 (61%) were hypertensive, and 11 (61%) were obese. On multivariate analysis, LNSF was not significantly associated with HbA1C, ALT or BP, while LNSE was negatively associated with HbA1C ($P=0.04$) but not with BP or ALT. When the ratio of LNSF to LNSE was studied, there was no significant effect on metabolic parameters. Late night salivary cortisol is more sensitive than salivary cortisone as a diagnostic test for CS and may identify cases of cyclical ACTH secretion. We did not identify an association between LNSF and metabolic parameters influenced by hypercortisolemia. The negative association between LNSE and HbA1C requires further elucidation.

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P812

Is elevated urotensin II level a predictor for increased cardiovascular risk in subjects with acromegaly?

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Purpose
Acromegaly, an uncommon disease, is existed in the result of over production of growth hormone (GH). It is associated with increased cardiovascular risk factors and metabolic abnormalities. Urotensin II (UII), a secreted vasoactive peptide hormone, plays an essential role in the regulation of vascular tone, glucose metabolism and atherosclerosis. UII belonging to somatostatin superfamily activates somatostatin receptors as well. The aim of this study was to ascertain whether circulating UII levels are altered in subjects with acromegaly and to describe the relationship between UII and hormonal or cardio-metabolic parameters.
Methods
This cross-sectional study included 41 subjects with active acromegaly, 28 subjects with controlled acromegaly and 37 age- and BMI-matched controls without acromegaly. Hormonal and metabolic features of the subjects as well as carotid intima media thickness (cIMT) and epicardial fat thickness (EFT) were defined. Circulation of UII levels was determined via ELISA.
Results
Both active and controlled acromegalic subjects showed a significant elevation of circulating levels of UII with respect to controls. There was no remarkable difference in circulating levels of UII between active and controlled acromegalic groups. Both cIMT and EFT were remarkably increased in acromegaly subjects comparing to controls. UII positively correlated with cIMT, EFT, BMI and HOMA-IR. There was no correlation between UII and GH, insulin-like growth factor-1. According to the results obtained from regression models, UII levels independently predicted cIMT and EFT.
Conclusion
Elevated UII levels are associated with severity of cardiovascular risk factors including cIMT and EFT in acromegalic subjects.

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P813

The association between Ki-67 proliferation index, P53 expression, mitotic index, tumor invasion and the risk of recurrence in pituitary adenomas

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Background
The 4th edition of World Health Organization (WHO) classification of pituitary tumors recommended evaluation of tumor proliferation and invasion to identify aggressiveness. We aimed to assess the relationship between Ki-67, mitotic index, P53 expression, invasion and recurrence risk in pituitary adenomas.
Methods
Among 601 patients who underwent TN/TS adenomectomy between 2001 and 2016, 101 patients (16.8%) who had tumors with Ki-67 index ≥ 3 were included and categorized as Group A. The control group (Group B) consisted of 43 patients matched for age, gender and tumor type but had Ki-67 index $<3\%$. Mitotic index and p53 expression were evaluated in 81 tumors. Histopathology reports, pre/postoperative radiological findings, tumor type, recurrence of tumors were assessed retrospectively.
Results
The mean age of patients was 46.9 ± 12.7 years. The most frequent symptoms were visual disturbances (34.7%). Frequency of somatotroph, mammotroph, gonadotroph, ACTH-producing, TSH producing, non-secreting and plurihormonal tumors were 35.4%,20.1%, 16%, 12.5%, 2.8%, 11.8% and 1.4%, respectively. Mean tumor size was greater in Group A compared to Group B (25 ± 10.6 vs 18 ± 11 mm, $P<0.01$) and frequency of macroadenomas was higher in Group A (67.4% vs 94.1%, $P<0.01$). Frequency of invasion to adjacent tissue was higher in Group A when compared to Group B (75.8% vs 22%, $P<0.01$). Fifty-one tumors had invasion to adjacent tissue at MRI and the most frequent invasion site was cavernous sinus (58.8%). The mean follow-up period was 46.6 ± 34 months. One hundred seventeen patients who had postoperative MRI and follow-up data for at least 12 months were evaluated and recurrence risk was higher in Group A patients than Group B ($P=0.03$). Ki-67 index ≥ 2.7 was positively associated with recurrence risk. Frequency of recurrence was higher in adenomas with invasion at preoperative MRI ($P=0.03$). Tumor size and recurrence were not associated with P53 expression. High P53 expression was related with tumor invasion at MRI ($P=0.03$). Tumors with high ($\geq 2\%$) mitotic index was more frequent among macroadenomas ($P<0.05$). Mitotic index was not associated with tumor recurrence risk and invasion. Recurrence risk was higher in tumors with ≥ 2 histopathological atypia criteria ($P=0.01$).
Conclusions
High Ki-67 index is a reliable marker for predicting recurrence in pituitary adenomas. Recurrence risk is higher in tumors with two histopathological atypia criteria and invasion.

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P814

Pituitary enlargement due to the autoimmune thyroiditis mimicking a pituitary macroadenoma

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Introduction
Pituitary tumorous hyperplasia with hyperprolactinemia has been described as a rare presentation of primary hypothyroidism. The loss of thyroxin feedback inhibition in primary hypothyroidism causes overproduction of thyrotropin-releasing-hormone (TRH), which results in secondary pituitary enlargement. TRH has a weak stimulatory effect on the lactotroph cells of the pituitary, so a mild to moderate increase in prolactin (PRL) levels is expected. This report describes an unusual case of primary hypothyroidism with pituitary hyperplasia mimicking a pituitary adenoma.
Case report
A 27 year old female patient admitted to the gynecology clinic with the complaint of infertility. A pituitary macroadenoma and mild hyperprolactinemia were detected after laboratory and radiological assessment and patient was referred to Endocrinology outpatient clinic. She had regular menstrual cycles and no galactorrhea. There were also no neurological symptoms such as headaches and visual disturbances. The patient had no known chronic disease and was not using any medication. Her hormonal profile showed raised thyrotrophin stimulating hormone (TSH) (44 μIU/ml, range 0.40–4.5) and low free T4 (0.78 ng/dl, range 0.88–1.72) and mildly elevated PRL levels (39.4 ng/ml, range: 5–25). The growth hormone and pituitary-adrenal axis were interpreted as normal. Magnetic resonance imaging (MRI) of pituitary showed 10×15 mm globular pituitary enlargement with a convex superior margin. Anti-thyroglobulin antibodies (>1300 IU/ml, range: 0–157) is found elevated while antimicrosomal antibodies was negative. Thyroid gland had a heterogeneous echotexture on the ultrasonography. A diagnosis of autoimmune thyroiditis and primary hypothyroidism with pituitary hyperplasia was suspected. Oral levothyroxine substitution treatment was started and the dose was increased gradually until euthyroidism was restored. After 6 months of follow-up, TSH and PRL levels dropped to their normal ranges and the pituitary enlargement was found regressed on MRI.
Conclusions
Pituitary enlargement secondary to primary hypothyroidism is known but uncommon entity and sometimes differentiation of pituitary gland enlargement from pituitary adenomas may be difficult. Interpretation of a pituitary mass without proper endocrine evaluation can lead to mismanagement and unnecessary treatment.

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P815

Intracranial germinoma with panhypopituitarism in a 18-year old patient

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Intracranial germ cell tumors (GCTs) account for only 0.4–3.4% of all central nervous system (CNS) tumors. A 18 year old patient with an unremarkable medical history was presented to the ophtalmology outpatient clinic with a 2 month history of loss of vision at left eye and blurrred vision at right also headache and fatigue. Ophtalmological examination showed loss of visual acuity at left eye and decreased 0.05–0.1 at the right and bilateral optic atrophy. Further physical examination showed sexual infantilism (poor beard, pubic and axillary hair growth, small testis). The patient's skin was dry and pale. Endocrinological examination showed panhypopituitarsm. Pituitary MR imaging demonstrated contrast enhancing mass lesion at suprasellar cisternal region which outstrecthed to posterior perimesencephalic cisternal region. The mass resected by craniotomy and pathology showed germinoma.Chemotherapy and radiation therapy were administered. He is still using prednisolon, L-thyroxine and human chorionic gonadotropin treatment.

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P816

Primary pituitary abscess: an unexpected diagnosis

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Pituitary abscess is a rare condition, with approximately 200 cases reported in the literatüre. Two-thirds of pituitary abscess which occurs without any of the aforementioned risk factors are primary type while remaining are secondary type-abscess. A 58 year old female patient presented with fatigue, headache and loss of appetite for two months. Laboratory analysis showed high ESR and CRP levels also hypocortisolism, hypothyroidism, hypogonadism. Pituitary MRI showed a mass measuring 30x20 mm dense, cystic, lesion on T2 weighted coronal view, which caused enlargement in the sella turcica, suprasellar cistern obliteration, indistinguishable from the pituitary gland, pushing the stalk to the superior and right posterolateral. She has no visual defect on ophtalmological examination. TSE surgery was done and purulent material was seen intraoperatively. No tumor or other associated lesion was detected. Culture of the specimen was negative. The patient treated with metronidazole,ceftriaxone and linezolid for 2 weeks and 4 weeks of metronidazole, ceftriaxone and sulfamethoxazole/trimethoprim. Her headache, fatigue, loss of appetite resolved. After surgery hypopituitarism continued and treated with oral prednisolon and L-thyroxine therapy.

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P817

Diurnal melatonin profile in patients with pituitary adenomas

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Introduction
The role of the pineal gland and its hormone, melatonin, in the regulation of hypothalamo-adenohypophysial system activity is well known. At the same time, studies of the circadian rhythm of melatonin secretion in patients with pituitary adenomas are few in number, because the evaluation of pineal activity is not generally included in the clinical investigation of patients with pituitary tumors.

Aim
The present study analyzed the circadian diurnal melatonin profile, in patients with GH/prolactin (PRL) secretion adenomas.

Subjects and methods
Under investigation there were 69 patients aged 18–75 years with pituitary tumors: 52 acromegaly (ACRO) (female 32/male 20); 17 prolactinoma (PROL) (female 14/male 3), by comparing the results with those seen in 10 healthy controls. All the patients had active disease and were off treatment; none had overt hypopituitarism. Blood samples for GH and PRL were taken in fasting state. 6-Sulfatoxymelatonin (MT), the main melatonin metabolite, was determined by fluorometric assay by C. Druex in two separated urine portions: in the daytime (MTd) and nighttime (MTn) in the spring/autumn period. Data are given as M ± S.D., Me, [Mim – Max].

Results
Abnormally high serum levels of MT during the period of maximum light and abnormally low increases during the night were seen in 31/52 ACRO (GH-23.6 ± 24.1, Me = 14.0 [3.1-144.9] ng/l) and 12/17 PROL (PRL - 248.5 ± 551.4, Me = 61.2 [2.35 - 3857.9] ng/l) patients. Moreover, mean levels of MT were significantly lower in patients than in controls. In ACRO patients total diurnal MT (85.08 ± 62.65; Me = 70.3 [9.5–324.6] nmol/24 h) and MTd levels (43.04 ± 31.25; Me = 33.65 [6.3–155.4] nmol/24 h) were significantly higher comparing patients with PROL: MT total - 49.58 ± 20.71; Me = 53.2 [17.8–103.2] nmol/24 h, $P = 0.0001$; MTd – 30.0 ± 19.24; Me = 31.24 [5.4–82.5] nmol/24 h, $P = 0.03$. It was found that in ACRO patients with daily rhythm inversion of melatonin excretion (MT-Ratio night/day < 1), MTn level was also significantly higher in comparison with PROL: 28.4 ± 18.3, Me = 25.4 [3.2 – 77.8] nmol/24 h; 16.4 ± 5.8, Me = 16.7 [5.9 – 26.6] nmol/24 h, respectively; $P = 0.0003$.

Conclusion
This study demonstrates the existence of an altered pineal function in patients with pituitary tumors. Further studies will be required to establish the pathogenetic and prognostic significance of pineal disorders in neoplastic disease of the pituitary gland.

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P818

Diabetes insipidus due to hypothalamitis and infundibulo-neurohypophysitis

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Autoimmune hypothalamitis has been implicated in idiopathic central diabetes insipidus (DI) due to antibodies against vasopressin producing hypothalamic cells. Lymphocytic infiltration of hypothalamus has been reported in patients with lymphocytic hypophysitis (LH) manifesting as hypopituitarism with DI. These patients can also have other associated autoimmune diseases. Here, we report a case of a male patient who presented with headache, poor orientation, partial hypopituitarism, diabetes insipidus, and whose MRI findings revealed involvement of hypothalamus, posterior pituitary and infundibulum. 40 years old male patient was admitted to the hospital with symptoms of polyuria (8–10 lt/day), polydipsia, headache. Urine density was low (1005). Hormonal testing revealed low IGF1, testosterone, normal cortisole levels, but thyroid hormone levels were in the normal range with high TSH and anti-TPO levels. Response to LHRH and ACTH stimulation tests were normal. Sellar fossa and pituitary gland size, pituitary gland enhancement were normal at MRI. Increased T2 signal intensity in the optic chiasm, hypothalamus, infundibulum and contrast enhancement in the T1-contrasted series were noted. This finding is most visible in 2016, but regressed in 2017. As the lesion did not cause any visual symptoms and did not have features typical of tumors of the suprasellar area, and the patient did not give consent for a pituitary biopsy, a strict follow-up and see policy was chosen. Polyuria improved after oral administration of desmopressin 2 × 120 μg. We did not give steroid treatment, levothyroxin was administered for the subclinical hypothyroidism. The symptoms improved in six months without steroid treatment, anterior pituitary functions returned to normal. The lesion spared the anterior pituitary. Hence, it is speculated that anterior pituitary dysfunction could be consequent to either deficiency of hypothalamic releasing hormones due to the involvement of hypothalamic nuclei or microscopic involvement of anterior pituitary. He is still being followed with desmopressin and levothyroxin. As far as we know this is the first case of hypothalamitis and infundibulo-neurohypophysitis presenting with symptoms of DI and partial hypopituitarism. To conclude, in a patient presenting with headache, hypopituitarism and a suprasellar mass, hypothalamitis also should be considered in differential diagnosis. Because it is a self-limiting condition, close follow-up with clinical and laboratory testing can be

sufficient for most of the patients. But also according to the literature, these patients may benefit from course of steroid and immunosuppressive drugs

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P819

Age and severity of hyperthyroidism are determinants of thoracic vertebral fractures in patients with TSH-secreting pituitary adenoma

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Introduction
Osteoporosis and vertebral fractures (VFs) commonly occur in overt and subclinical primary hyperthyroidism. In this clinical setting, bone damage is caused by the direct effects of thyroid hormone in excess on bone remodeling, although there is also evidence that low thyrotropin (TSH) values may play a role in driving fracture risk. In fact, TSH was shown to have direct inhibitory effects on osteoclastogenesis and bone resorption. Based on these data, one could argue that primary and secondary hyperthyroidism may induce variable effects on bone in relationship to the different TSH values. In this cross-sectional study, we evaluated for the first time the prevalence and determinants of VFs in patients with TSH-secreting pituitary adenoma (TSH-oma).
Patients and Methods
Twenty-two patients (10 M, 12 F; median age 47.0 years) with TSH-oma were retrospectively evaluated for clinical and biochemical parameters as well as for thoracic VFs using a morphometric approach on lateral chest X-ray routinely performed in the pre-surgical diagnostic work-up.
Results
At the time of VFs assessment, 17 patients (77.3%) had an overt hyperthyroidism and five patients (22.7%) had thyroid hormone values in the reference ranges. TSH values were inappropriately normal in 17 patients and high in five patients. VFs were found in 13 patients (59.1%) in association with older age ($P=0.007$) and higher serum free-thyroxine (FT4) values ($P=0.02$). The prevalence of VFs was more frequent in patients with overt hyperthyroidism as compared to those with thyroid hormones in the reference ranges (70.6% vs. 20.1%; $P=0.04$), whereas no significant difference was found in patients with high vs. normal TSH values ($P=0.38$).
Conclusions
This study provides for the first time evidence that patients with TSH-oma may develop VFs in close relationship with the severity of hyperthyroidism. It is likely that elevated TSH levels do not protect bone in TSH-omas due to the predominant negative effect on bone of elevated circulating thyroid hormones.

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P820

Cushing disease after remission and prevalence of cardiovascular risk factors

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Objective
Cardiovascular risk factors (CVRF) persist with notable prevalence in patients with Cushing's disease (CD) after remission: obesity/overweight up to 40%, hypertension (HTA) up to 60%, type 2 diabetes (DM-2) up to 60% and dyslipidemia up to 30% of cases. Persistence of metabolic syndrome in patients with controlled CD seems to be related to the duration of the disease before remission. The aim of this study is to describe the prevalence of CVRF in patients with CD in remission.
Patients and methods
Retrospective descriptive study of patients with CD (1995–2016). Variables analyzed: age, sex, body mass index (BMI), CVRF at diagnosis and after the remission of CD, treatment of CVRF. Statistical analysis (SPSS v.18.0 for Windows): t-student for comparison of means and McNemar for comparison of proportions.
Results
49 patients with CD. Age 44.43 ± 15.29 years. Women: 89.8%. Transsphenoidal surgery: 87.8%. Remission: 68.7%. Time from onset of clinical to diagnosis: 29.7 ± 30 months. At diagnosis of CD: 36% obesity and 16% overweight, 20% DM-2 [treatment with oral antidiabetics 40%: 20% metformin, 20% sulfonylureas; 60% insulinized (insulin dose 26 ± 16 IU/day)], 68% HTA (54% antihypertensive treatment with more than one drug) and 36% dyslipidemia. After remission of CD: 27% obesity ($P=0.8$), 25% overweight ($P=0.7$), 15.3% DM-2 persisted ($P=0.9$) [oral antidiabetics 100% (75% metformin and 25% metformin and secretagogue)], 46% HTA ($P=0.3$) and 50% dyslipidemia ($P=0.5$). BMI at diagnosis 32 ± 8 kg/m^2, after remission 30 ± 5 kg/m^2 ($P=0.8$).
Conclusions
CD is more frequent in the fourth decade of life and is more frequent in women. The prevalence of obesity, DM-2 and HTA is reduced after remission of CD, increasing the prevalence of overweight and dyslipidemia, without statistically significant differences.

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P821

Clinical relevance of metabolic phenotype in hypopituitarism: what really matters?

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Previous studies reported increased prevalence of metabolic syndrome (MS) and mortality rates from cardiovascular causes in hypopituitary patients. Fatty liver disease was added recently to this unfavorable cardio-metabolic phenotype. We studied the prevalence of MS and non-alcoholic fatty liver disease (NAFLD) in unselected cohort of 282 hypopituitary patients (146 male), mean age 49.2 ± 15.1 years, on standard replacement therapy (76.4% received l-thyroxin, 76% hydrocortisone, 9.8% gonadal steroids, 4.6% desmopressin, 1.8% growth hormone). Surrogat marker of MS, lipid acummulation product (LAP) was calculated using gender specific formulas including waist circumference and triglyceride level. Marker of NAFLD, fatty liver index (FLI) was calculated using formula including body weight, height, waist circumference, triglyceride and gamma glutamyl transferase levels. Hepatic steatosis was assessed by ultrasonography and liver function tests. In this cross-sectional study, prevalence of MS was 57.1% (using IDF) and 48.6% (with ATP III criteria). MS was more common in females than males (IDF 63.2% vs 51.4%, $P=0.044$; ATP III 54.4% vs 43.2%, $P=0.059$) and significantly associated with unreplaced hypogonadism in female patients ($P=0.003$). Statistically significant associations ($P<0.001$) were found for MS and age, obesity, adult onset of hypopituitarism and NAFLD. Prevalence of NAFLD in the cohort was 20.6%, based on ultrasonographic features of hepatic steatosis, while in addition to this 7.1% had elevated liver enzymes. For NAFLD, statistically significant associations were found with MS ($P<0.001$), etiology of non-functioning pituitary macroadenoma ($P=0.006$) and growth hormone deficiency ($P=0.026$). Hypopitutary patients with NAFLD had more severe features of MS with significantly higher body mass index, waist circumference, cholesterol and triglycerides, LAP and FLI, but lower HDL compared to no-NAFLD patients ($P<0.001$). ROC analysis confirmed that LAP and FLI were reliable markers of hepatic steatosis and functional hepatic impairment resulting from NAFLD. MS is common in hypopituitarism, featuring NAFLD in one third of hypopituitary patients with MS. Hypopituitary NAFLD patients present with more severe MS and higher LAP and FLI indexes compared to no-NAFLD patients. LAP and FLI are reliable markers of hepatic steatosis and functional hepatic impairment, resulting from NAFLD. Complex interactions of multiple pituitary hormone deficiencies and balance in their replacement are very important for metabolic phenotype, as well as age, gender, obesity, adult onset and etiology of hypopituitarism.

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P822

TSH-secreting pituitary adenomas: clinical and morphological characteristics and outcomes of surgical treatment

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Objective
To study the clinical, diagnostic and morphological characteristics and treatment outcomes of TSH-secreting pituitary tumors.
Patients and methods
The study included 21 patients with pituitary adenoma and a normal or elevated TSH level and elevated fT_4 and fT_3 levels who were operated on at the Neurosurgical Institute in the period between 2002 and 2015. Before surgery, in the early postoperative period, and 6 months after surgery, the patients were tested for levels of TSH, fT_4, fT_3, prolactin, cortisol, LH, FSH, estradiol/testosterone, IGF-1. The thyroid status was evaluated using the following reference values: TSH, 0.4–4.0 mIU/l; fT_4, 11.5–22.7 pmol/l; fT_3, 3.5–6.5 pmol/l. An immunohistochemical study of material was performed with antibodies to TSH, PRL, GH, ACTH, LH, FSH, and Ki-67 (MiB-1 clone); in 13 cases, we used tests with antibodies to somatostatin receptors type 2 and 5 and to D2 subtype dopamine receptors.
Results
TSH-secreting tumors were detected in patients aged from 15 to 67 years (median 39 years), males (48%) and females (52%). Before admission to the Neurosurgical Institute, 11 (52%) patients were erroneously diagnosed with primary hyperthyroidism; seven of these patients underwent surgery on the thyroid gland and/or received thyrostatics (four cases). Hyperthyroidism symptoms were observed in 16 (76%) patients. The level of TSH was 2.47–38.4 mIU/l (median, 6.56); fT_4, 22.8–54.8 nmol/l (median, 36); fT_3, 4.24–12.9 pmol/l (median, 9.66). Tumors had the sellar localization in 4 (19%) cases and the parasellar localization in 17 (91%) cases. Total tumor resection was performed in 7 (33%) patients. All these tumors had the sellar and suprasellar localization. No total resection was performed in patients with infiltrative growth of adenoma (invading the skull base structures). An immunohistochemically study of tumor resection specimens detected TSH expression in 21 (100%) cases; 18 (86%) tumors were plurihormonal and secreted TSH and GH and/or PRL. Of 13 tumors, expression of the type 2 dopamine receptor was detected in 9 (69%) cases; expression of somatostatin receptors type 5 and type 2 was found in 6 (46%) and 2 (15%) cases, respectively.
Conclusion
The criterion for total tumor resection was a postoperative TSH level decrease to 0.1 mIU/l or less. Total resection was performed in 33% of patients with sellar and suprasellar tumors only. In most cases, tumors were plurihormonal secreting TSH and GH and/or PRL.

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P823

Recovery of the adrenal function after pituitary surgery in patients with Cushing Disease: remission or recurrence?

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Background
The treatment of choice in patients with Cushing Disease (CD) is pituitary surgery (PS). A successful PS is generally followed by adrenal insufficiency (AI). Although the remission rate after PS may reach 96.6% of cases, approximately 1/3 of cured patients experience the recurrence of the disease during lifetime. The aim of this study was to analyze the duration of AI in relation with the recurrence of CD.
Materials and methods
We performed a retrospective analysis on patients with CD followed at our center between 1995 and 2017 and who met the following inclusion criteria: age above 18 years, presence of adrenal insufficiency 2–3 months after PS and a minimum follow-up of 3 years. Adrenal insufficiency was confirmed on either basal cortisol <3 μg/dl or a cortisol peak <18 μg/dl during consynthropin test (1 mcg or 250 μg). Recurrence was defined by high urinary free cortisol (UFC) levels and a positive dexamethasone suppression test (1 mg overnight or 2×2 mg: cortisol >1.8 mg/dl).
Results
According to the inclusion criteria we selected 54 patients. The mean follow-up was 6.6 years (median: 5 years, interquartile range (IQR): 4–9.25 years). The recurrence rate at 3 years was 11.1% (6/54) while the cumulative rate was 14.8% (8/54). Six out of eight patients experienced the recurrence in the first 3 years after PS, one patient at 4 years and one after 15 years. AI recovery rate without disease recurrence was 35.3% at 3 years with a cumulative rate of 48.8%. Comparison between the two groups (remission/recurrence) showed a similar gender ratio (F:M = 8:1), BMI (25.4 ± 4.1 vs.27.7 ± 6.6, $P=0.4$), age at PS (43.5 ± 16.1 vs 41.5 ± 14.3 years, $P=0.7$). Also hormonal characteristics and radiologic features did not show any significant difference between the two groups. The duration of AI was the only parameter significantly different (median 24.3, IQR: 11.9–40 vs 10.7, IQR: 8.1–17.2). In particular, the recovery time of adrenal function represented a significant predictor for persistent remission (OR: 1.14, CI: 1.003–1.313, $P=0.046$). Using the duration of AI as diagnostic test for persistent remission we observed a good accuracy (AUC 0.91, $P<0.001$). The persistence of AI after 22 months had a PPV of 100% and NPV of 47% for persistent remission.
Conclusion
Our study show that the duration of adrenal insufficiency after PS in patients with CD may be a useful predictor for persistent disease remission.

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P824

Hypothalamic involvement in diffuse large B-celllymphoma

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Non-hodgkin lymphoma (NHL) is a hematological tumor caused by abnormal lymphoid proliferation. NHL can arise in any part of the body, including central nervous system (CNS). However, hypothalamus involvement is a rare presentation. Here, we report a case of hypothalamic infiltration of NHL Diffuse Large B-cell lymphoma (DLBCL) in a 21 years old male patient with panhypopituitarism and diabetes insipidus. The patient was admitted to the hospital with a history of nausea, vomiting, headache, asthenia, quickly worsening walking impairment and weight loss in two months. He denied neck stiffness and fever. Neurological examination showed global motor slowing, generalized weakness against resistance to head and limbs, no sensitive deficit or focal neurologic sign was recognizable. Hormonal evaluation revealed panhypopituitarism. Non-contrast computed tomography (CT) of the head was performed in the emergency department, showing hydrocephalus and a suprasellar mass. At further imaging a soft tissue mass with a maximum diameter of 14×16 mm on the axial plane, which was located in the infundibulum, optic chiasma and hypothalamus and extending into the third ventricle was also discovered with magnetic resonance imaging (MRI). Ependymoma, metastasis to the hypothalamus, primitive neuroectodermal tumor was speculated for differential diagnosis. Anterior and posterior pituitary was preserved. Lumbar puncture, blood tests, including serology for HIV and other infections, were negative. He was operated and immune histopathological examination of the specimen revealed DLBCL. He was treated with chemotherapy (rituximabe, methotrexate) and cranial radiotherapy. During hospitalization, hypotension, polydispsia, polyuria were observed. Hormonal and clinical evaluation was compatible with central diabetes insipidus and panhypopituitarism. He is still being followed with desmopressin, dexamethasone, levothyroxin and testosterone. The incidence of primary central nervous system lymphoma (PCNSL) has been increasing in recent years, accounting now for 2–6% of all intracranial tumors, although it is considered an uncommon aggressive tumor. Most PCNSL is diffuse large B-cell lymphoma ($>95\%$) whereas T-cell lymphomas are rare. Clinical presentation and imaging findings can vary according to the immune status of the patient. In order to treat the disease optimally, early diagnosis is important. In conclusion, hypothalamic infiltration of NHL on MRI is a rare finding. Diagnosis should be suspected after biochemical analysis and MRI results. Treatment consists of chemotherapy against NHL and hormonal replacement for pituitary dysfunction.

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P825

Iceberg alert: undetected health problems in adults with Prader-Willi syndrome – multidisciplinary care could prevent 'unexplained deaths'

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Introduction
A yearly mortality rate of 4% among young adult patients is unacceptable in any patient population. Nevertheless, in Prader-Willi syndrome (PWS), up to 4% of young patients die every year and this situation has been going on for decades. PWS is a complex hypothalamic disorder, combining hypotonia, intellectual disability (ID), pituitary hormone deficiencies and hyperphagia. Due to this lack of satiety, patients can literally eat themselves to death: overeating can cause morbid obesity, complicated by diabetes and secondary cardiovascular complications, or stomach rupture. The mean age of reported deaths in PWS is 29.5 years; 20% of deaths even occur below age 18 years and mortality is often unexpected. Autopsy reports show that in some cases, the cause of death is food-related, like gastrointestinal perforation and aspiration/choking due to rapid consumption of food. However, in half of the patients, the cause of death turns out to be cardiovascular origin or obesity-related respiratory failure. These severe complications can be prevented if Prader-Willi associated obesity is managed effectively in a multidisciplinary setting.
Methods
In order to optimize care for patients with this complex syndrome, we have launched a multidisciplinary outpatients clinic (OPC) for adults with PWS, consisting of an endocrinologist, an ID-physician, a physiotherapist, an ID-dietitian and a neuropsychologist. We have analysed the clinical data of the patients who visited the multidisciplinary OPC including medical histories and physical and biochemical measurements.
Results
Among the first 90 patients visiting the multidisciplinary OPC, we found a striking number of undetected and untreated health problems, like untreated hypogonadism (also present in lean PWS adults), untreated osteoporosis, untreated diabetes, untreated hypothyroidism and obesity. Although half of the patients was obese, 23% of patients exercised less than 30 min per day and one third was not on a diet. Caregivers often reported stealing and merchandising for food, meaning that diets are doomed to fail unless carefully supervised. Nevertheless, 25% of patients lived under incompetent supervision.
Conclusion
During the first two years of the multidisciplinary OPC, we detected a striking number of untreated health problems among adults with PWS. Most patients have at least 3 serious health problems. The combination of complex health issues among adults with PWS requires multidisciplinary care. The multidisciplinary OPC for adults with PWS will prevent painful and expensive complications and reduce mortality in this vulnerable patient population.

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P826

Pituitary apoplexy in pregnancy lead to empty sella

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Pituitary apoplexy (PA) is an endocrine emergency characterized by acute, severe headache, visual disturbances, ophthalmoplegia, hypopituitarism and altered consciousness. This condition usually arises in an underlying pituitary adenoma. 27-year-old female without a known pitutary lesion presented to the emergency department in December 2015 with a 8-hour history of with sudden and severe frontal headache, fever, blurred vision, nausea, confusion at 36 weeks of gestation. The past history revealed that the patient had normal periods after puberty and no galactorrhea before pregnancy. Nothing was notable from her medical or family history; she did not smoke and was not taking any drugs.On admission her laboratory evaluation was revealed secondary hypothyroidism, and secondary adrenal insufficiency (Table 1).Non-contrast MRI demonstrated a macroadenoma, 2.2×2.1 cm in size with apoplexy and there were significant suprasellar extension and compression of the optic apparatus. The patient was admitted to the intensive care unit and put on intravenous steroids. She reported a dramatic improvement in her vision and headeche within 24 h after steroids treatment. After five days of hydrocortisone treatment L-thyroxine 25 μg/day treatment was given for secondary hypothyroidsm which dose increased gradually. She was treated conservatively and the clinical picture improved in a few days, followed by an uneventful pregnancy and delivery. Six month after delivery MRI report revealed empty sella and endocrinological investigation revealed secondary gonadal, thyroid and adrenal insufficiency (Table 1). Patient used hydrocortisone 20 mg/day and L-thyroxine 100 μg/day.
Conclusion
Pituitary apoplexy is a rare condition and it may manifest as the first presentation for the preexisting pituitary tumor.

Table 1 Endocrinological Evaluation

	On admission	6 monts after delivery	Normal reference value
ST4 (pmol/l)	9.0	16.5	12–22
TSH (mIU/ml)	0.064	0.151	0.4–4.2
PRL (ng/ml)	352	467	4.79–23
GH (ng/ml)	0.187	0.675	
IGF-1 (ng/ml)	298	287	116–358
Cortisol (nmol/l)	175	138	171–536
ACTH (pg/ml)	<5	<5	0–46
FSH (IU/l)	<0.1	<0.1	3.5–12.5
LH (IU/l)	<0.1	0.158	2.4–12.5

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P827

Benefits of pre-surgical treatment with somatostatin analogs in naive patients with acromegaly

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Introduction
Somatostatin analogs (SS-analogs) are the treatment option when there is a persistent disease despite surgical intervention. They can be also recommended as a first line treatment if surgery is not appropriate (non-curative or contraindicated surgery).
Objetive
To evaluate the effect of first-generation SS-analogs (lanreotide and octreotide) on tumour shrinkage and biochemical control in naive patients.
Methods
We performed a prospective study of 23 acromegalic patients (followed between years 2000 and 2015) treated with SS-analogs awaiting surgery. We evaluated mean age, associated comorbidities, growth hormone (GH), insulin growth factor 1 (IGF1), and prolactin (PRL) mean levels, also tumour volume (TV) and maximum tumour diameter (MTD) reduction, and repercussion of SS-analogs in the glicaemic metabolism; baseline and after 6 months of treatment. The differences between groups were calculated by Wilcoxon test.
Results
The mean age at diagnosis was 48±13 years, 39% men and 61% women. 87% were macroadenomas. BMI was 26±4 kg/m^2. Hypertension was found in 47%, glicaemic metabolism disorders in 47%, dyslipidemia in 26%, obstructive sleep apnea hypopnea syndrome in 17%, carpal tunnel syndrome in 30%. 57% of patients received high doses of SS-analogs, 34% medium doses and 9% low doses. 26% received concomitant treatment with cabergoline. After 6 months of treatment, we found significant differences in: MTD (18±9 previous vs 15±9 mm, $P=0.001$), TV (3098±4,829 vs 2,362±5,005 mm^3, $P=0.001$), GH levels (30±28 vs 12±20 ng/ml, $P=0.003$), IGF1 levels (1182±461 vs 661±50 ng/ml, $P=0.000$) and PRL levels (29±33 vs 7.4±5.4 ng/ml, $P=0.001$). After 6 months of treatment: 26% normalized IGF1, 13% had GH levels under 1 ng/ml and 61% achieved a TV reduction ≥ 20%. We did not find significant differences in glicaemic metabolism after receiving treatment with SS-analogs (glycemia 119±37 vs 114±17 mg/dl, $P=0.74$ and HbA1c 6±0.9 vs 6.1±0.8%, $P=0.66$).
Conclusions
Our results demonstrate the clinical benefit, in biochemical control and tumour shrinkage, of SS-analogs as a primary treatment for patients with acromegaly.

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P828

Temozolomide is effective for rapid control of hypercortisolism in aggressive acth-secreting pituitary tumors

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Background
Temozolomide is an alkylating chemoterapic agent that ties a methyl to guanine, causing a base-pair mismatch and a DNA damage, resulting in cell death. Due to its lipophilic nature and its ability to cross the blood-brain barrier, this drug was originally used for malignant gliomas and later for aggressive pituitary tumors and carcinomas. Temozolomide is now recommended as first-line chemotherapy by the recently published ESE Clinical Practice Guidelines. Here we present our experience with temozolomide in three patients with aggressive and invasive ACTH-secreting pituitary tumors.
Patients
PT1 (female, 65 years-old) after two surgical interventions (pathology: ACTH-staining pituitary adenoma) and several medical therapies, underwent a severe relapse in hypercortisolism associated with worsening of general conditions and increase in tumor remnants. Temozolomide was started, leading to a sudden control of hypercortisolism. One month later PT1 underwent gamma-knife radiosurgery. Temozolomide was withdrawn after five cycles for hematological side effects. After 5 years, hypercortisolism is still in remission and a signisficant reduction in tumor remnants was documented. PT2 (male, 50 years-old) a few months after pituitary surgery (pathology: ACTH-staining pituitary atypical adenoma, Ki-67 > 4–5%) underwent severe relapse of hypercortisolism; temozolomide (in association with capecitabine, 'CAPTEM') was started with pasireotide, leading to a rapid control of disease. Six months later PT2 was treated with external-beam radiotherapy. CAPTEM was withdrawn after 12 cycles, pasireotide was withdrawn 1 month later and hydrocortisone was started for the development of hypocortisolism. PT3 (male, 50 years-old) had been treated with four surgical interventions and a course of external-beam radiotherapy. MRI revealed tumor remnants in the right cavernous sinus and above the sellar region, compressing the right subnuclear and temporo-mesial regions and the right-inferior cerebellar pedunculus; furthermore a meningeal metastasis was spotted above the clivus, protruding in the prebulbar cysterna. PT3 underwent 15 cycles of CAPTEM gaining an overall good control in hypercortisolism and a reduction in tumor and metastasis size. PT3 remained in remission of disease for 3 years.
Conclusion
Therapy with temozolomide (alone or in combination with capecitabine) was highly effective in controlling hypercortisolism in the short term; moreover, in association with radiotherapy, temozolomide proved effective in reducing pituitary mass and prolonging remission of disease. It can be considered for different categories of patients: patients (as PT1) with severe/repeated recurrence of disease; patients (as PT2) with histologically aggressive tumors in whom surgery was not complete and hypercortisolism relapses; patients (as PT3) with pituitary carcinoma.

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P829

Cancer in acromegaly: a case-control study

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Carcinomas are the third most frequent cause of complications in acromegalic patients. It has been suggested that diabetes potentiates the risk of cancer. To assess the frequency and type of malignant neoplasms in acromegalic patients and control group; to evaluate, in both groups, the relationship between IGF-I/GH and the development of cancer, and between glucose metabolism and cancer in two centers of Buenos Aires, Argentina. Retrospective, cross-sectional study; medical records of patients with acromegaly and control group with pituitary illnesses with normal GH/IGFI, sex- and age-matched, 1985–2017, were reviewed in order to find information about the presence of any neoplastic diseases. Sixty-two acromegalic patients, 50% women; 51 controls, 55% women; mean time of follow-up was 10.2 years. Mean age of acromegalic patients and control group was: 59 ± 14 vs 58 ± 15 years. Nine acromegalic patients (14.5%) developed cancer; mean age when cancer appeared was 59 ± 14 years. In two patients both diseases were simultaneously diagnosed; in the remaining patients the mean time between the diagnosis of acromegaly and cancer diagnosis was 15.7 years. The types of cancer were: colon in three male patients (33%), prostate in 2 (22%), testicular teratocarcinoma in one, breast in one female, papillary thyroid carcinoma in one female, kidney in one male. IGF-I and GH at cancer diagnosis were elevated in three patients and normal in six. Eight patients had altered glucose metabolism, only one had normal glucose levels. In the control group, four patients developed cancer (7.8%), mean age when cancer appeared was $59 \pm$ 24 years, and the types of cancer were: in two men lymphoma and lung cancer; in two women rhabdomyosarcoma in mediastinum and colon cancer. None of these patients had altered glucose metabolism. The relative risk of developing cancer in acromegalic patients was 1.85, IC 95% 0.65–5.66. When we compared the disturbance of glucose metabolism in both groups with cancer, acromegalic vs control, it was 88,9% vs 0.0% ($P = 0.007$), respectively. In acromegalic patients, among those who developed cancer and those who did not, the glucose metabolism disorders were 88.9% vs 35.8% ($P = 0.008$), respectively.
Conclusions
In our study, the risk of developing cancer in acromegalic patients was 85% higher than in the control group. Although this trend is important, statistical significance was not reached due to the small sample size. In acromegalic patients, cancer was significantly associated with disturbance of glucose metabolism.

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P830

A rare case of acromegaly with normal IGF-1, severe chronic congestive heart failure, and impaired glucose tolerance

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Introduction
Acromegaly with normal IGF-1level is rarely diagnosed and is difficult to recognize. In acromegalic pa-tients with poorly controlled diabetes, malnutrition, hepatic injury, hepatic congestion due to heart fail-ure, inflammatory diseases, renal dysfunction, and malignant neoplasm, IGF-1 synthesis is inhibited and thus in such cases normal IGF-1 levels may be observed. The aim of the study is to present a rare case of a patient with acromegaly and normal IGF-1 level, and to emphasize that low or normal concentrations of IGF-1 do not rule out the diagnosis of acromegaly.
Case report
A 75-year-old woman with pituitary macroadenoma was admitted to hospital with suspected acromegaly. The pituitary tumor was visualized 24 years earlier during CT performed because of headaches. 1 year later, without hormonal evaluation, the patient was disqualified from the neurosurgical treatment. For 23 years she had performed only periodic imaging controls. In 2012 CT revealed a focal lesion 17×15 mm within the Turkish saddle, suggesting the presence of craniopharyngioma. 28 years ago the patient had undergone partial thyreoidectomy due to nodular goiter. She also suffered from long-term arterial hypertension resistant to treatment, chronic heart failure, atrial fibrillation with ventricular extrasystolia and severe osteoarticular disorders. She had thickened facial features, enlarged tongue, hands and feet, and increased sweating. Basal GH level was 10.37 ng/ml (n:0.03–2.47) without GH suppression during OGTT (3.79 ng/ml, $n: < 0.4$), IGF-1 = 157.3 ng/ml (n: 29–204). The remaining pituitary functions were normal. On the basis of OGTT [96 mg%–150 mg%] an impaired glucose tolerance was diagnosed. In MRI pituitary tumor $17 \times 19 \times 14$ mm was detected. Renal insufficiency, malnutrition [BMI = 34.2 kg/m^2] or malignant neoplasms were excluded. Acromegaly was diagnosed and Lanreotyd Autogel 120 mg every 28 days was introduced. Because the patient refused neurosurgery, she remains on long-acting somatostatin analogue therapy.
Conclusion
Probably the low concentration of IGF-1 in the presented case was caused by liver damage secondary to long-term severe congestive heart failure, most likely caused by long-term untreated acromegaly and hyperglycemia.

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P831

Two-dimensional speckle tracking echocardiography showed a slight impairment of left ventricular deformability in acromegalic patients at diagnosis and during follow-up

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Introduction
Acromegalic heart disease is characterized by concentric left ventricular (LV) hypertrophy and impaired LV function. Speckle tracking echocardiography (STE) allows a non-invasive and reproducible study of myocardial strain, a marker of cardiac deformability and early ventricular systolic dysfunction.
Objectives
The aims of the study are: 1) evaluation of STE parameters in acromegalic patients at diagnosis and during the follow-up; 2) appraisal of the role of hypertension, diabetes or both on the STE parameters in acromegaly; 3) assessment of the impact of biochemical control and different treatments for acromegaly on global LV longitudinal strain (GLS) and other echocardiographic features.
Patients and methods
It was an historical-prospective study enrolling 111 acromegalics and 54 matched subjects with non-functioning pituitary adenoma used as controls. All subjects underwent clinical and biochemical evaluations and two-dimensional echocardiography using STE. LV mass index (LVMi), LV ejection fraction (LVEF), E/A ratio, and GLS were obtained. 53 patients were evaluated at diagnosis of acromegaly; 21 of them were also longitudinally reassessed after reaching disease control. 79 subjects were evaluated during the follow-up and classified according to treatment for acromegaly: adenomectomy ($n=11$), somatostatin analogs (SSA, $n=43$), Pegvisomant (Peg, $n=16$), SSA + Peg ($n=9$). 69/79 subjects appraised during the follow-up had complete control of acromegaly at the time of STE evaluation.
Results
At diagnosis, mean LVMi was increased and mean E/A ratio was decreased in acromegaly compared to controls (*t* test; $P=0.03$ and $P=0.009$, respectively). The mean GLS differed between acromegaly and control group at diagnosis (t-test; -18.12 ± 0.43 vs. -19.55 ± 0.35, $P=0.01$). The presence of hypertension, diabetes or both did not affect GLS at diagnosis of acromegaly (ANOVA, $P=0.81$). Any differences in LVMi, EF, E/A ratio, and GLS were observed during follow-up, either stratifying patients with biochemical disease control or the basis of the type of therapy. In the group of subjects evaluated longitudinally, GLS improved in 12 and worsened in nine after the achievement of disease control even if the mean GLS value did not significantly change (paired *t* test $P=0.62$).
Conclusions
Acromegalic patients are characterized by concentric LV hypertrophy and diastolic dysfunction at diagnosis. GLS study showed, for the first time, slight impairment of cardiac deformability in naive acromegalic patients that was not influenced by the presence of hypertension and diabetes. The therapies and the biochemical control of acromegaly do not seem to influence myocardial strain in acromegalic patients.

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P832

Trabecular bone score as skeletal fragility predictor in patients with acromegaly

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Introduction
Several studies have demonstrated a high incidence of vertebral fractures (VF) in acromegaly, not always correlated with bone mineral density (BMD) value adquired by dual X-ray absorptiometry (DEXA). At trabecular level, GH may alter bone microarchitecture (BM) that predisposes to bone fragility. Trabecular Bone Score (TBS), a textural parameter applied to DEXA to evaluate BM, could be useful to predict VF risk in these patients.
Materials and methods
A cross-sectional study was carried out in acromegalic patients followed up at our hospital between 1989 and 2016. DEXA with Horizon DXA system (Hologic®) to assess lumbar (L1-L4) BMD and TBS value (TBS iNsight®), spine X-ray and blood tests to evaluate hormonal status and bone metabolism were performed. DXA and TBS results were compared with a healthy control group. TBS ≥ 1.35 corresponded to a normal BM (NBM), 1.2-1.35 to a partially degraded BM (PDBM) and ≤ 1.2 to a degraded BM (DBM).
Results
Twenty-six acromegalic patients meeting criteria of disease control by IGF1 levels (53.8% women; age 59.3 ± 15.6 and median BMI 28.4 kg/m^2) and 128 control subjects (53.1% women; age 50.9 ± 20.3 and median BMI 24.9 kg/m^2) were evaluated. TBS was lower in patients compared with control (1.26 ± 0.13 vs 1.35 ± 0.18; $P=0.01$), with no significant differences in BMD (g/cm^2), T-score and Z-score (0.99 ± 0.2 vs 0.96 ± 0.15; -0.63 ± 1.76 vs -0.95 ± 1.35 and 0.41 ± 1.67 vs -0.22 ± 1.44 respectively). In acromegalic patients no significant relationships were found between IGF-1, gonadal and adrenal status, TBS and lumbar BMD. Patients who had received radiotherapy (RT) had lower TBS than those who had not (1.15 ± 0.08 vs 1.31 ± 0.13; $P=0.017$). DBM was observed in 80% of acromegalic patients with diabetes mellitus vs 22% in non-diabetics ($P=0.05$). VF were found in 3 patients, all of them with TBS values corresponding to DBM (TBS 1.09, 1.2 and 1.08).
Conclusions
In our study, acromegalic patients show lower TBS than healthy controls, particulary in RT-treated and diabetic subgroups. This finding suggests alterations in BM that could explain the increased risk of fractures in these patients. More studies are needed, exploring the fracture predictive capacity of TBS in these patients.

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P833

Registry for central diabetes insipidus in Russia: prevalence and etiologies of the disease

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Introduction
Epidemiological data for central diabetes insipidus (CDI) are quite sparse.
Objectives
To provide an epidemiological data on CDI in different regions of Russia (20 from 83 Federal regions).
Materials and methods
We used the Russian Registry for Central Diabetes Insipidus (RCDI) to study the epidemiological features of CDI.
Results
A total of 2004 patients with CDI were recorded, 47% women and 59% men. The most common of identified etiologies for CDI were postoperative (13,1%), head trauma (7,4%), and pathology of development of hypothalamic-pituitary region (6,9%). Less common were tumors (4,3%) and hereditary forms of CDI (4,3%). Rare forms of CDI with less than 4% overall were neuroinfection, Langergans hystiocytosis, sarcoidosis, and Sheehan syndrome. Idiopathic CDI was considered in 37% of patients, which is lower than previously reported 51%. The prevalence between participating in RCDI regions was variable from 0,65 to 10,67 cases per 100 000 population. The prevalence in Moscow city which represents a multinational population was 4,5% per 100 000 population. Nine from 20 regions have higher prevalence than that in Moscow city, with 4 of them having the prevalence twice as higher which may represent ethnic differences.
Conclusions
There is a reduction of previously reported proportion of idiopathic form of CDI which represent a progress in diagnostics. High variability in prevalence of CDI may represent ethnic differences.

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P834

Two cases of silent corticotroph adenomas

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Introduction
Pituitary adenomas are mostly benign tumors which may be clinically functioning or non-functioning and ACTH secreting tumors make up 15% of them. Up to 20% of corticotroph adenomas which don't have any biochemical or clinical evidence of hypercortisolism are known as silent corticotroph adenomas.
Case 1
A 54 years old male presented with blurred of vision and headache that increasing in severity within six years. Physical examination and visual field tests were normal. After initial evaluation, the brain MRI was performed and pituitary mass was detected 33x27x28mm diametered, heterogeneous in nature, extented to suprasellar region, infiltrates cavernous sinuses and contact with optic chiasma. Pituitary hormones were in normal range except high serum ACTH level. Twenty four hour urine free cortisol level and dexamethasone supression test are within normal range and physical examination did not show any cushingoid signs. Transnasal transsphenoidal surgery was performed and pathology reported as "densly granulated corticotroph adenoma, Ki 67: %3, p53 (-)".
Case 2
A 55 years old male admitted to hospital with a complaint of headache. Past medical history includes prior pituitary surgery, depression and hypertension. His arterial tension and neurologic examination was normal. Prior pituitary pathology report could not be reached. After first evaluation he underwent to brain MRI that revealed pituitary adenoma about 12x10x5mm in diametered, no sign for extension to optic chiasma and cavernous sinuses. Pituitary hormones were in normal range except high serum ACTH level. Twenty four hour urine free cortisol level and dexamethasone supression tests were in normal range, patient had also no cushingoid signs. Transnasal transspheonidal surgery was performed and pathologic examination revealed "corticotroph staining adenoma as Ki 67: %2 and p53 (-)".
Discussion
Cushing's disease are detected in 0.7 to 2.4 per million individuals per year. Most of the corticotroph adenomas are microadenomas. Silent ACTHomas are generally >1 cm in diameter. It is difficult to differentiate pre-perioperatively. Most of silent adenomas don't exhibit any hormonal and physical abnormalities except for serum ACTH level. But serum ACTH level is not enough alone to diagnose Cushing's disease. It is thought that high-measured ACTH is immunologically active but biochemically inactive. So clinicians must be avoided to make wrong diagnosis. Clinicians also should keep in mind that sometimes silent adenomas cause subclinical Cushing diseases during progression of disease and most of them are difficult to remove surgically because of extension to surrounding tissue.

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P835

IgG4-related neuroinfundibulo-hypophysitis treated by rituximab and corticosteroids

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IgG4-related hypophysitis, a type of IgG4-related disease, is a rare condition. It appears to be sensitive to glucocorticoids in most patients, but its recurrence is likely.
Clinical case
A 17 year-old girl was referred for hypotonic polyuria and polydipsia of 1 month duration. Water deprivation test was suggestive of central diabetes insipidus. Basal and dynamic assessment of pituitary anterior function were unremarkable. Patient did suffer from autoimmune thyroiditis and autoimmune gastritis. Serum IgG4 were found high [269 mg/dl (49-66)] as well as serum IgE [2600 U/ml (50-120)]. Magnetic resonance imaging (MRI) of the sella turcica showed a clear enlargement of the pituitary stalk with an intense and homogeneous contrast enhancement, the neurohypophysis bright spot, on pre-contrast images, could not be identified. IgG4-related neuroinfundibulo-hypophysitis was suspected on clinical grounds. Imaging studies, such as total body positron emitted tomography and abdomen ultrasound, excluded other localization of disease.B-cell depletion therapy with Rituximab was administered (1 g iv for two doses in 14 days), preceeded by metilprednisolone pulse therapy. Oral therapy with metilprednisolone, started at 40 mg/d, was continued for 6 months. To control polyuria, desmopressin was started at 180 mcg/d.Three months after first treatment, control MRI showed a normal sized pituitary stalk with normal enhancement after gadolinum, serum IgG4 and IgE were reduced (60% and 30%, respectively) although still above normal range. After 6 months, at the end of metilprednisolone therapy, sellar MRI still showed a normal pituitary and stalk. IgG4 and IgE were decreased, pituitary anterior function was normal. Diabetes insipidus was still present, however the dose of desmopressin needed to control polyuria was lower than at diagnosis (60 mcg/d).
Conclusion
IgG4 related hypophysitis is a rare condition that may benefit from B-cell depletion therapy. Goal of treatment is remission of pituitary inflammation and ultimately of diabetes insipidus. Careful follow-up is needed in order to spot recurrence of the disease, in the pituitary or in other sites.

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P836

Early postsurgery cortisol after transphenoidal surgery to predict adrenal insufficiency one year posturgery

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Aim
To assess a perioperative glucocorticoid protocol in transsphenoidal surgery (TSS)and the performance of early post-TSS 08:00 cortisol measurement to detect/exclude secondary adrenal insufficiency.
Methods
We selected patients undergoing TSS.In patients with no cushing disease, we checked cortisol/Synachten presurgery, measured 3° postoperative 0800 a.m. cortisol(after 24 h without corticoids) and cortisol/Synachten 3-6 months post-surgery. We excluded patients with previous diagnosed and treated adrenal insuficiency.All included patients received perioperative glucocorticoid replacement (First and second days postsurgery) unless basal cortisol was >10 mcg/dL and cortisol after Synachten >23 mcg/dL previous to surgery (In these patients we measured cortisol in 1 day postsurgery). All patients with cushing disease received perioperative glucocorticoid. In patients with 1°/3° day cortisol lower than 15 we maintained glucocorticoid treatment until reevaluation with cortisol/Synachten 6 months post-surgery.In patients with 1°/3° day cortisol higher than 15 glucocorticoids were discontinued. We evaluated again patients after one year of surgery.
Results
Data were obtained from 52 patients (55,7% women, mean age 46,7+/-15,6 years), Mean tumour size:20.1+/-11.9 (5-51 mm). Diagnosis:40.4% non functioning adenomas, 17,3% acromegaly, 26,9% cushing disease, 7.7% prolactinoma, 7.7% others. 72.4% of patients were treated with glucocorticoids perioperative. Patients with adenomas no cushing: 85% of patients with 1°/3° day cortisol $>$ 15mcg/dL had normal cortisol/Synachten 6 months post-surgery vs 20% of patients with 1°/3° day cortisol <15 ($P<0.05$). After one year of surgery: 88,2% of patients with 1a/3° day cortisol >15mcg/dL had adrenal sufficiency, 40% of patients with 1a/3° day cortisol between 10 and 15 and 50% of patients with <5 mcg/dL had adrenal sufficiency. 9.1% of patients with adenomas <20 mm had adrenal insufficiency vs 46.2% of patients with adenomas >20 mm (100% if patients had other presurgery deficiencies) ($P<0.05$). None of the patients without perioperative glucocorticoids had adrenal insufficiency symptoms during perioperative period. Cushing disease: all patients with 3° day cortisol $<$ 5mcg/dL are in remission 1 year after surgery vs 33,3% of patients with 3° day cortisol >5 mcg/dL ($P<0.05$)
Conclusion
A 3° day post-TSS cortisol $>$ 15mcg/dL is a safe cutt off to discharge adrenal insufficiency. 100% of patients with 3° post-TSS $<$ 5 mcg/dL are in remission 1 year postsurgery. Our protocol to select patients who need or not perioperative glucocorticoids is safe to manage patients with TSS.

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P837

Cushing's disease with negative or inconclusive MRI: reassessment of transphenoidal surgery at the age of medical treatment. Post operative remission rate in 184 patients including 86 with negative or inconclusive MRI

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When pituitary MRI show a typical imaging of adenoma, it is agreed that transsphenoidal surgery is the reference treatment with remission achieved in about 80% of patients. If MRI is negative or inconclusive, some authors consider that the results of surgery are less successful, and propose medical treatment as a first line therapy, despite a disease control rate between 30 and 70%. Since 1990, our center chose to systematically explore patients with ACTH dependent hypercorticism by a Bilateral Inferior Petrosal Sinus Sampling (BIPSS) when MRI is negative or inconclusive, and to perform transphenoidal neurosurgery when BIPSS demonstrates that ACTH is of pituitary origin. The remission data and the characteristics of the adenomas were retrospectively collected from the computerized medical file of all our patients operated for Cushing's disease between 1992 and 2016. Our main objective was to evaluate the performance of neurosurgery in Cushing's disease in patients with normal or inconclusive MRI versus MRI with a typical adenoma image. 184 patients were operated: 82 microadenomas, 16 macroadenomas, 43 with inconclusive MRI and 43 negative MRI. The postoperative remission rates were not statistically different, 85.4%, 93.7%, 72.1% and 74.4% ($P=0.119$) respectively. A crude cost analysis comparison between expert neurosurgery and medical treatment shows that in our country the cost of drugs to treat only one patient for Cushing's disease for 30 years is equivalent to the cost of exploration and treatment of 30 to 60 patients in an expert center for pituitary surgery and neuroradiology. We conclude that even at the age of medical treatment neurosurgery in an expert center should be the first line therapy of patients with Cushing's disease and a negative or inconclusive MRI.

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P838

Simultaneous coexistence of Cushing's disease and renal cell carcinoma

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Background
After the diagnosis of corticotropin (ACTH) dependent Cushing's syndrome established, its cause must be determined. Cushing's disease (CD) is caused by corticotropin (ACTH) secreting adenomas and it accounts for roughly 75-80% of all endogenous Cushing's syndrome. These adenomas are almost always benign. Renal cell carcinoma (RCC) is the most seen kidney cancer. In this case report, a presentation of a patient who was diagnosed with concurrent CD and RCC was planned.
Case
A 40-year-old patient admitted to our hospital with complaint of abdominal pain. Abdominal MRI performed in the urology department revealed a 7.5x7 cm mass in the left kidney, which showed a close proximity to adrenal gland. Left partial nephrectomy was performed. Pathologic evaluation revealed papillary renal cell carcinoma. Tumor diameter was 6x5x4 cm. Positron emission tomography showed no pathological metabolic activity in the lymph nodes. There was no metastatic finding. She was referred to our polyclinic with the suspicion of Cushing's syndrome. She was diabetic and she had been using oral antidiabetic drugs for 4 years. On her physical examination she had findings of Cushing's syndrome. 1 mg dexamethasone suppression test was performed with the suspicion of Cushing syndrome. No suppression of cortisol levels was observed in the result of the test (cortisol level = 17 μg/dL). Cortisol levels were also higher than the reference values in 24 hour urine cortisol test. Basal ACTH was 47 pg/mL. Other anterior pituitary hormones were normal. The patient was evaluated as CD. Magnetic resonance imaging (MRI) of the sella revealed a 14x10 mm sized adenoma. Optic chiasm was normal. The patient underwent transsphenoidal surgery. Monitoring of the patient is continued.
Conclusions
In this case ectopic ACTH syndrome should be considered in differential diagnosis. Various tumors can cause ectopic ACTH syndrome. Small cell lung carcinoma, carcinoid tumors, islet cell tumors, pheochromocytoma and medullary thyroid carcinomas are the most frequent tumors. In ectopic ACTH syndrome circulating ACTH and corticol levels are extremely high, the duration of symptoms is short and the clinical phenotype is different from CH. The ectopic ACTH syndrome was excluded because of the presence of the pituitary adenoma, the fact that the ACTH levels were not too high and the phenotypic findings of the patient were incompatible with the ectopic ACTH syndrome. This case illustrates the importance of considering differantial diagnosis between ectopik ACTH syndrome and Cushing's disease accompanying renal cell carcinoma.

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P839

The relationship between sleep apnea syndrome and metabolic parameters in patients with acromegaly

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Background
Acromegaly is a rare endocrine disorder characterized by sustained hypersecretion of growth hormone (GH) with concomitant elevation of insulin-like growth factor I (IGF-I) associated with acral enlargement, sleep apnea, cardiovascular and metabolic disorders. Its annual incidence is approximately six per million people. The most common cause of acromegaly is a somatotroph (growth hormone-secreting) adenoma of the anterior pituitary.
Methods
A total of 28 patients diagnosed with acromegaly were included in this retrospective study. Seventeen of the patients were female and 11 of them were male. The clinical presentations, anthropometric measurements, fasting and postprandial blood glucose levels, triglyceride levels and polysomnography characteristics of patients were analyzed. The patients were divided into two groups according with and without sleep apnea syndrome.
Results
The mean age of these patients was 50.60 ± 13.92 years and 15 (53.6%) of the patients were sleep apnea syndrome. Of these patients, 63.6% of the women; 47.1% of the men had sleep apnea syndrome. 46.4% of patients with sleep apnea syndrome were diabetic. 66.7% of the patients without diabetes, did not have sleep apnea syndrome. As a result, a statistically significant difference was found between diabetic patients with and without sleep apnea syndrome ($P<0.05$). Serum triglyceride levels were examined when patients were diagnosed with acromegaly. Serum triglyceride levels were 161.53 ± 59.10 mg/dl in the group with sleep apnea syndrome and $99.15 \pm 38{,}58$ mg/dl in the group without sleep apnea syndrome. There was a statistically significant difference in serum triglyceride levels between these two groups ($P<0.05$).
Conclusion
In this study, we investigated the association of sleep apnea syndrome with metabolic disorders in acromegaly patients. It's revealed that diabetes and hypertriglyceridemia are more frequent in patients with sleep apnea syndrome in acromegaly.

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P840

Early postoperative GH level as biomarker for surgical outcome in patients with acromegaly

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Introduction
Persistence after transsphenoidal surgery remain a significant challenge in management of acromegaly. Value of basal growth hormone (GH) evaluation in early postoperative period as marker of acromegaly persistence has been proposed and discussed in the literature, but is not widely used in clinical practice.
Aim
The goal of our study is to specify the value of basal GH level measurement 24 hours later after transsphenoidal surgery as postoperative biomarker for surgical outcome in patients with acromegaly.

Materials and methods
A total of 18 patients (12 women and 6 men) with an average age of 48.9 ± 13.5 years (range 27-66 years) were enrolled in our study. All patients underwent total transsphenoidal adenomectomy performed by one neurosurgeon. All patients harbored macroadenomas, with average size of 18.3 ± 4.9 mm (range 11-29 mm). Measurement of a 24-hours postoperative GH level was performed in all patients. The outcome of surgery via OGTT and measurement of insulin-like growth factor 1 (IGF-1) was evaluated 6 months after surgery. The biochemical remission of acromegaly according to the 2010 remission criteria are defined as nadir GH level on an OGTT <0.4 μg/l along with age and gender normalized values of IGF-1.
Results
At baseline basal GH level was 36.4 ± 23.5 μg/l, IGF-1 was 2.5 ± 0.6 times the upper limit of normal. At 6 months after surgery, the remission of acromegaly was achieved in 8 patients (44%). A 24-hours postoperative GH level in patients with remission was 1.4 ± 0.5 μg/l, whereas in group with acromegaly persistence –5.3 ± 1.7 μg/l. All patients with persistence of the disease had a 24-hours postoperative GH level $\geq$ 2.0 μg/l.
Conclusion
Our study suggests that a 24-hours postoperative GH level above 2.0 μg/l associated with persistence of acromegaly 6 months after surgery.

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P841

Optimal follow-up strategy based on the natural history of nonfunctioning pituitary adenomas

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Object
The natural history and proper algorithm for follow-up testing of nonfunctioning pituitary adenomas (NFPAs) are not well known, despite their relatively high prevalence. The aim of this study was to suggest the optimal follow-up algorithm for NFPAs, based on the natural history.
Methods
We followed up on 197 patients with NFPAs without any treatment (including surgery and radiation) at the time of detection, in a single center, between March 2000 and February 2017. We conducted a hormone test, visual field test and magnetic resonance imaging (MRI) at the time of diagnosis, and then, yearly.
Results
The overall median follow-up duration was 37 months. Microadenomas (n = 38) did not cause visual disturbance, pituitary apoplexy, or endocrine dysfunction. The incidence of patents with a 120% or larger tumor volume growth was higher in macroadenomas than microadenomas (13.8% vs. 5.0% per year). The overall incidence rate of worsening visual function was 0.69% per year. Patients with a tumor volume growth rate $\geq$ 0.35 cm^3/year (n = 38) showed higher incidences of worsening visual functions (3.52% vs. 0.16% per year) and endocrine dysfunction (4.40% vs. 0.49% per year). Based on the tumor volume growth rate, the median time for 10% of patients to grow more than 120% was 3.4 years in microadenomas and 1.9 years in macroadenomas.
Conclusion
The tumor volume growth rate was the strongest predictor of worsening visual functions or endocrine dysfunction. A follow-up strategy needed to be determined based on the tumor volume growth rate as well as initial tumor volume.

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Pituitary – Clinical

P842

Thicknesses of Chorioretinal layers in Prolactinoma Patients: A Spectral Domain Optical Coherence Tomography Study

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Introduction
Prolactinoma is a type of pituitary tumor that produces excessive amount of the hormone prolactin. It is the most common type of hormonally-active pituitary tumor. These tumors can result in ocular complications such as vision loss and visual fields (VF) defect. In this study, we aimed to evaluate thicknesses of chorioretinal layers in patients with prolactinoma.
Material and method
We enrolled 21 prolactinoma patients (13 females, 8 males and mean age: 40.7 ± 8.1 years) and 18 age and gender matched healthy controls. All participants underwent complete hormonal and ophthalmological examination including thicknesses of chorioretinal layers and VF test. We used the Spectralis spectral domain optical coherence tomography for evaluation of chorioretinal layers in an outpatient setting. The seven layers were retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE). Additionally, we calculated the mean thickness of two combined layers: inner retinal layer (IRL) and photoreceptor layer (PL). The results of prolactinoma patients were compared with the control group.
Results
There were no statistically significant differences in median right-left and mean RNFL, GCL, IPL, INL, OPL, ONL, and IRL measurements between prolactinoma and control groups ($P > 0.05$ for each). Median right and mean RPE were significantly low in the prolactinoma group ($P = 0.018$ and $P = 0.028$, respectively). Median right-left PL was similar in two groups, while mean PL was significantly lower in patients with prolactinoma compared to control group ($P = 0.04$) None of the patients had VF defect. When we compared two subgroups of prolactinoma patients (active/inactive), we found that the thicknesses of layers were not significantly different between the groups.
Conclusion
To our knowledge, this is the first study that evaluates thicknesses of chorioretinal layers in patients with prolactinoma. Thicknesses of many layers were similar with control group, while mean RPE and PL were lower in prolactinoma group.

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P843

Combined treatment of craniopharyngiomas

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Introduction
Craniopharyngiomas (CF)- benign epithelial tumors that develop from the remnants of Rathke's pouch cells. Most often, CF manifest themselves in two age groups: in children 5–14 years old making 5.6–13% of intracranial tumors and in adults 50–74 years old making 2–5%.
Materials and methods
In the last decade, the Institute annually for the surgical treatment received 100–120 patients with CF. The total number of cases (given and repeated) exceeds 2500. For transcranial removal of CF we use different combinations of basal and transcallosal approaches. In pediatric patients this type of surgery reaches 60%, and in adult patients only 20%. Starting in 1987 we use transsphenoidal approaches (first microsurgically, from 2005 pure endoscopicaly). Extended endoscopic approach makes possible radical tumor removal. Now transsphenoidal operations for CF in pediatric group takes only 20%, instead 60% in adults. For cystic craniopharyngiomas in some cases, we use Ommaya systems. It takes 20% of both pediatric and adults group.
Results
In recent years, mortality in adults group after tarnscranial surgery does not exceed 8%, after transshenoidal and Ommaya system in both age groups mortality is zero. Tumor recurrence after total and subtotal removal takes 21.5%, and after a partial takes 53.2%. The recurrence rate of papilomatouse CF takes 7.8%. In the last decade we started using radiosurgery and stereotactic radiotherapy ("Gamma knife", "Cyber knife", "Novalis"). In cystic CF after irradiation we saw sharp reduction in production of cystic fluid. Nowadays we do not have sufficient statistics to estimate the effect of irradiation on the rate of tumor progression and the probability of formation of its recurrence, but we have the number of cases with significant reduction of tumor size.
Conclusion
Further development of a combined treatment of CF will be to improve surgical techniques such as endoscopic assistance in transcranial surgery and improvement of transsphenoidal endoscopic techniques. Future analysis of the effect of different variants of radiotherapy on recurrence rate will optimize surgical removal of CF, as well as irradiation regimes. Modern morphological studies will identify CF subgroups with the aggressive character of growth and a high risk of relapse.

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P844

Vitamin D status in acromegaly: a comparative study

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Background
The vitamin D is a pleiotropic hormone that plays a significant role on global health. However, vitamin D status in acromegaly has been poorly studied.
The aim
The aim of this study was to assess the vitamin D status in acromegaly and compare it to a control group. Then to analyse bone remodeling and density markers based on the vitamin D levels.
Methods
We conducted an evaluative cross sectional study in the Department of Endocrinology at the National Institute of Nutrition in Tunis comparing 2 groups of 25 acromegalic patients and 25 control subjects (age and sex matched).
Results
The average age was 50 ± 14.52 years [16–52]. The sex ratio was 9/16 (36% men and 64% women). The mean duration of the acromegaly was 8.6 ± 9.62 years. As for acromegalic repercussions patients presented with rheumatologic impacts in 80% of the cases, visual in 72%, respiratory in 68%, pituitary in 56%, metabolic in 56% and tumoral in 8%. Twenty-one subjects underwent surgical treatement, 24% were under somatostatin analogs, two patients had received radiotherapy. Acromegaly was active in 64% of the cases, controlled for 4 patients and cured for 5 (20%). The vitamin D status was similar between the acromegalic group and the control subjects: Thirteen acromegalic patients had deficiency, 9 (36%) had insufficiency and 3 patients (12%) had a normal level of vitamin D. The univariate study showed that, duration of sun exposure, exposed surface, score screening for vitamin D insufficiency, height, PTH, and GH were significantly associated with the vitamin D level in acromegalics.
Conclusion
The exploration of the vitamin D status in acromegaly should become a common practice. The management starts with the prevention of the defict, the screening and eventually a therapeutic supplementation.

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P845

Hypernatraemia and mental disorders

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The problem of the influence of disturbances of Hyper- or Hyponatraemia is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. Electrolyte disbalance affected on the formation of mental disorders, their structure and dynamics in the literature has not been sufficiently studied. Perhaps there are certain factors and patterns of the influence of hypo- and hypernatraemia on mental activity with various lesions of the brain, which requires study.
Purpose
To study the effect serum sodium concentration on the structure and dynamics of mental disorders on the model of a benign tumor of craniopharyngioma.
Material and methods
89 patients (18–65 years old, mean age 38 ± 2, 44 men and 45 women) were examined after removal of craniopharyngiomas in the early postoperative period. Methods: psychopathological, data from endocrinological, neurological, neuroimaging methods of research were used. Serum sodium concentration was determined in the norm of 135–145 mmol/l.
Results
1 group – 43 patients (48%) with hypernatraemia after removal: endo-suprasellar (10%), suprasellar (35%), extra-intraventricular (45%) and intraventricular (10%) craniopharyngiomas. Group 2 – 46 patients (52%) with normal serum sodium concentration after removal: endo-suprasellar (39%), suprasellar (37%), extra-intraventricular (11%) and intraventricular (13%) craniopharyngiomas. Analysis of mental disorders in patients revealed productive symptoms in 80%: motor excitement, affective disorders, delirium, visual hallucinations, amnestic confusion. These disorders occurred in patients with hypernatraemia more often ($P < 0.001$) (group 1) than in patients with normal serum sodium concentration (group 2). In the first group there was a subgroup of patients with persistent long hypernatraemia (lasting more than 5–7 days) in 22 patients (51%). In this subgroup there were negative (deficient) symptoms: Korsakov's syndrome, apathy, increased drowsiness in 15 patients (68%). It was significantly more frequent ($P < 0.001$) compared to patients with normal serum sodium concentration.
Conclusion
Serum sodium concentration affects a person's mental activity. Hypernatraemia can be a factor that causes productive symptoms and syndromes of mental disorders and adversely affects their dynamics, that it was revealed in patients after removal of craniopharyngiomas.

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P846

The use of colonoscopic screening in acromegaly in our everyday practice revisited: how compliant with guidelines have we been?

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Introduction
Although it has been suggested that there is a strong association between acromegaly and premalignant colonic lesions and colon cancer, it seems that in real – life practice the adherence to ACRO colonoscopy guidelines might be lower than expected (as recently shown by M.Parolin et cols).
Methods
We retrospectively reviewed the case records of the 54 patients with acromegaly seen in our center since 1994.We analyzed the findings of 27 patients who had undergone full length colonoscopy.
Results
Only 50% of our patients underwent at least one colonoscopy. 34 colonoscopies were performed since 1994 and the total number of colonoscopies increased from 0 in the period of 1994–1999, to 9 in the period of 2000–2005, and to 21 between 2012 to 2017.25% of the colonoscopies were performed at diagnosis and 75% during follow up. Diverticulosis and internal hemorroids were the most frecuent findings. In 33% of the screened patients (9/27) polyps were found. Among these patients 7 were women and 2 were men with a median age of 60.5 years (42–79) and a median IGFI level of 343,4 (126–761). A total of 18 polyps were found with a median size of 5 mm (2–11 mm), and the adenomatous polyps being the most frequent type. Pathological specimen results were Hyperplastic polyp (5/18), tubular adenoma (10/18), tubulovillous adenoma (1/18), villous adenoma(1/18), serrated adenoma (1/18). 1 female patient had colon adenocarcinoma (3.7%, 1/27). No complications related to the endoscopic examination were reported, such as perforation or bleeding.
Conclusions
The compliance to the guidelines in our center has been low with an increasing adhesion over the years. We do not know the reasons behind this change, but we are aware that due to the findings in our series, we will work towards a more proactive surveillance and improve the adherence to the guidelines.

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P847

The Secret of the Ophtalmopathy

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Although the first line therapy for prolactinoma is medical. Visual field defect due to pituitary mass would lead to surgery. Herein, we share the post-operative follow-up of a macroprolactinoma case.
Case
A 57-year-old male patient was operated on for a giant pituitary adenoma, which was compressing the optic chiasm. The postop prolactin (PL) value was found to be higher than 200 ng/ml and cabergoline treatment was initiated. Two months after the operation, the patient was admitted to the hospital for complaints of exophthalmos, headache, fatigue and drowsiness. Blood pressure was 100/60 mmHg, laboratory values revealed Na 128 mEq/l and creatinine 1.82 mg/dl. Adrenal insufficiency was presumed and methylprednisolone was initiated. Cranial CT scan was obtained to exclude secondary complications of operation, and it revealed a 1.5 cm residual adenoma and pseudotumor orbita. When the persistent microscopic haematuria, elevated sedimentation rate (ESR) (80 mm/s) and proteinuria (1.3 g/24 h) were considered, with the clinical finding

of pseudotumor orbita, it was believed that all would be indicative of vasculitis and IgG4 related diseases. ANA was negative, PR3ANCA was 3(+) and IgG4 was 224 mg/dl (120–200). Steroid treatment resulted in a significant improvement of ocular and biochemical findings (creatinine 1.4 mg/dl, ESR 36 mm/h). We performed kidney biopsy to exclude Wegener granulomatosis (WG). Biopsy was compatible with WG; IgG4 staining was negative. Pulse steroid therapy and 1 g cyclophosphamide were administered. Haematuria disappeared, IgG4 normalized, creatinine and ESR decreased to 0.9 mg/dl and 29 mm/s, respectively. Cabergoline treatment was switched to bromocriptine to exclude the cabergolin induced vasculitis.

Conclusion

The patient did not have retroorbital biopsy, on the other hand the kidney biopsy supported WG. It has been reported that the PL elevation triggers autoimmunity and clinical remission can be achieved by treatment with dopamine agonist in patients with SLE and RA, whose PL levels are elevated. There are cases in which IgG4 related diseases were identified by the initiation of high dose cabergoline treatment and the relationship between IgG4-related diseases and WG has been firmly stated in the literature. Under the light of literature, vasculitis may have been triggered by prolactinoma and cabergoline treatment in our patient. The orbital pseudotumor may be associated with either IgG4-related disease or WG. A few cases have been reported about WG-associated pseudotumor orbita in adult patients. In this respect, our case remains exciting.

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P848

Tolvaptan usage in hyponatremic patients with syndrome of inappropriate secretion of antidiuretic hormone: a single-center experience

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The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a disorder of impaired water excretion caused by inability to suppress secretion of antidiuretic hormone. The therapy of SIADH varies with severity of hyponatremia and presence or absence of symptoms. Non-peptide vasopressin receptor antagonists (vaptans) are effective at increasing sodium in euvolemic and hypervolemic states and appear safe. We aimed to evaluate the efficacy of tolvaptan in euvolemic hyponatremic patients with SIADH.

Methods

The study included 13 euvolemic hyponatremic (serum sodium level <125 mmol/l) patients with idiopathic SIADH between January – December 2017. The diagnosis of SIADH was made with hyponatremia, hypoosmolality, urine sodium level above 40 mEq/l and urine osmolality above 100 mosmol/kg. Serum potassium levels of all patients were normal, there was no acid-base disturbance. Patients with hypervolemic or hypovolemic status and hepatic dysfunction were excluded from the study. All patients received 7.5 mg/day of tolvaptan therapy. Clinical and laboratory data of patients were obtained before and after treatment.

Results

The mean age of patients (11 females, 2 males) was 74.6 ± 10.9 years (range 57–95). There was type 2 diabetes mellitus in 5 (38.5) patients, hypertension in 12 (92.3%) patients and chronic kidney disease in 7 (53.8) patients. The mean sodium levels before tolvaptan treatment were 120.5 ± 2.2 mmol/l (range 116–124). The mean sodium levels increased to 132.6 ± 4.0 mmol/l (range 125–140) after tolvaptan treatment at 2.7 ± 1.3 days (range 2–6). This increase in the sodium levels was significant ($P<0.001$). In a patient, hyponatremia recurred after ten days and corrected with two doses of tolvaptan. We did not observe serious adverse event related with tolvaptan treatment.

Conclusion

Our study suggested that hyponatremia was a common problem in elderly patients who had co-morbidities. Tolvaptan can treat hyponatremia effectively and safely in euvolemic elderly patients with SIADH.

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P849

Real-world data from NordiNet International Outcome Study (IOS) and ANSWER Program provide new insights into the safety of growth hormone in a large cohort of children with Noonan Syndrome

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Objectives

Congenital heart disease, especially pulmonary stenosis, is a frequent comorbidity in patients with Noonan syndrome (NS). Patients with NS are also at increased risk of childhood leukaemia and solid tumours. Among solid tumours, brain tumours, including glioneuronal tumours, have been described in younger patients but remain rare. Current safety data do not indicate an association of growth hormone (GH) therapy with increased risk for development or progression of tumours or worsening of congenital cardiac conditions, but available data are limited. This report describes long-term real-world safety data on GH therapy in paediatric patients with NS.

Methods

Two complementary non-interventional, multicentre studies, NordiNet IOS (NCT00960128; $n=154$) and the ANSWER Program (NCT01009905; $n=258$), evaluated the long-term effectiveness and safety of Norditropin (somatropin; Novo Nordisk A/S, Denmark) as prescribed by treating physicians in a real-life clinical setting. Safety data (serious adverse events [SAEs] [not related to therapy], non-serious and serious adverse drug reactions [NSARs/SARs]) were evaluated for GH-treated patients with NS ($n=412$) enrolled in these studies.

Results

Baseline characteristics (% or mean [SD]): female, 29.1%; age at treatment start, 9.48 (3.92) years, height standard deviation score (SDS), −2.65 (0.95), weight SDS −2.03 (1.31), insulin-like growth factor-I (IGF-I) SDS, −1.13 (1.62), IGF binding protein−3 SDS, −0.91 (1.72), GH dose (μg/kg/day), 43.9 (13.7), GH-naïve, 68.5%. Mean (SD) treatment duration, 3.1 (2.6) years. GH dose (μg/kg/day), during treatment, 46.6 (13.6). The most common cardiovascular comorbidities reported included pulmonary valve stenosis (20 patients) and atrial septal defect (five patients). Overall, 31 adverse events (AEs) were reported in 21 patients (#events/#patients): NSARs, 21/15, SARs, 2/1, SAEs, 8/5. Most patients with AEs reported one event (16/21). For patients with AEs, mean (SD) age at treatment start was 9.90 (4.13) years and height SDS at baseline was −3.14 (0.82). The most common NSARs were headache (six events/six patients) and arthralgia (five events/three patients). Two SARs (brain neoplasm; metastases to spine) were reported in one patient. The SAEs reported were giant cell epulis (one patient), scoliosis and spinal fusion surgery (both in one patient), moyamoya disease (one patient), glioneuronal tumour (one patient), and aggravated glioneuronal tumour and epilepsy (one patient). No cardiac AEs were reported.

Conclusions

These data further support a favourable safety profile of GH therapy in patients with NS, specifically the absence of any cardiac AEs. Glioneuronal tumours have previously been associated with Noonan syndrome and RASopathies.

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P850

Hypophysitis: Experience of a single tertiary center

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Purpose

The authors review the clinical outcomes of patients with hypophysitis.

Methods

Medical records of hypophysitis patients who were followed between 2007 and 2018 at Cerrahpasa Medical Faculty were evaluated retrospectively. Clinical, endocrinological, pathological and radiological findings and therapies were assessed.

Results

Twenty patients (F/M:12/8) were identified with a mean age at diagnosis of 39.14 ± 17.78 years. The mean follow-up was 34.23 ± 14.12 months. Eleven out of 20 patients (55%) were diagnosed histopathologically, 9 patients (45%) were diagnosed clinically with typical MRI findings. Five of 20 patients (25%) were

secondary hypophysitis: 3 histiocytosis-X, 1 neurosarcoidosis and 1 Erdheim Chester disease. From 7 histologically diagnosed patients with primary hypophysitis, 5(25%) had lymphocytic, 1(5%) had lymphocytic-granulomatous and 1 (5%) had xanthomatous hypophysitis. None of the hypophysitis cases were diagnosed after pregnancy. The most commonly seen symptoms are headache (65%), polyuria/polydipsia (45%) and fatigue (%30). Pre-treatment endocrinological evaluation revealed that 9 (57%) patients had panhypophysitis, 9 (45%) had diabetes insipidus, 6 (30%) had hyperprolactinemia, 7 (35%) had isolated endocrine deficiencies with partial gland function and 2 (10%) had normal laboratory values. Radiologic findings of patients at the time of diagnosis revealed various results including large sellar mass (65%), thickened infundibulum (50%), uniform contrast enhancement (40%), loss of hypophysis bright spot on T1 imaging (20%) and partial empty cella (15%). Six out of 15 primary hypophysitis patients were treated conservatively and six of them had been operated. The remaining 3 out of 15 and 2 patients who didn't have remission after surgery were treated with steroid therapy. Two patients, who needed to take steroid therapy after surgery and didn't have remission despite these treatment modalities had radiotherapy. Sixty-six percent (4/6) of patients who were on steroid treatment experienced avascular necrosis. Overall, 55% of patients had radiographic improvement and 45% had stable or deteriorated imaging findings. Endocrinological evaluations revealed that 1 patient (5%) had improvement, 16 patients (85%) had stable findings, 3 patients (15%) had deteriorated endocrinological functioning and 1 patient didn't have any follow-up data. Six patients who were followed conservatively had no sign of worsening radiologically or endocrinologically.

Conclusion

It is a challenge to make the right diagnosis and also the appropriate treatment of hypophysitis. It is unclear whether active treatment with steroids improves clinical outcome. When the serious side effects of steroids are also taken into account, surgery and or radiotherapy can be appropriate treatment modalities for selected patients.

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P851

Pituitary adenomas in childhood and the transition period - clinical and genetic characterization of 49 patients at one tertiary care endocrine institution in Romania

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Introduction

Pituitary adenomas (PAs) are rare in childhood and the transition period, can result from *AIP/MEN1* mutations, are difficult to manage and severely impair quality-of-life.

Aim

To describe the clinical and genetic characteristics of patients with PA onset before 21 years old.

Patients and methods

Retrospective study (1980–2015). Clinical, imaging and hormonal data, *AIP/MEN1* sequencing.

Results

We identified 49 patients (33 F/16 M), with onset age 18 (15–19) years, median (25th–75th percentile): 27 prolactinomas (5 micro, 20 macro, 2 giant adenomasn [>4 cm]; 3 clinical MEN1), 11 somatotropinomas (9 macro, 2 giant adenomas; 2 *somatolactotropinomas*; 2 patients with gigantism), 8 corticotropinomas (7 microadenomas), 2 nonfunctional PAs (NFPA, 1 mesoadenoma, 1 macroadenoma), 1 giant GH co-secreting, thyrotropinoma. From 34 patients tested, two (both with gigantism) had *AIP* mutations: c.940C>T (M-18yrs.), c.895dup (F-13yrs.). One patient with prolactinoma and primary hyperparathyroidism had a *MEN1* mutation: c.1446delC. Therapy included Dopamine agonists (DA): 27 prolactinomas, 8 somatotropinomas, 2 corticotropinomas, 1 NFPA, 1 thyrotropinoma; Somatostatin analogues: 11 somatotropinomas and 1 thyrotropinoma; Pegvisomant: 5 somatotropinomas; pituitary surgery: 10 somatotropinomas, 6 corticotropinomas, 1 NFPA, 1 thyrotropinoma; radiotherapy: 8 somatotropinomas, 3 corticotropinomas, 8 prolactinomas, 1 NFPA, 1 thyrotropinoma; Temozolomide: 2 giant PAs, multiply operated and irradiated (1 thyrotropinoma+1 DA-resistant prolactinoma). *AIP* mutations were associated with gigantism, giant adenomas ($rsquare = 0.59$, $P < 0.01$) and the absence of tumour growth control ($rsquare = -0.39$, $P < 0.05$). The number of treatment agents per patient was 1 (1–2), for prolactinomas and 5 (3–6) for somatotropinomas. At the last follow-up visit, 7 (2–10.5) years after diagnosis, 33/47 (70.21%) functional PAs were controlled biochemically.

Conclusions

Results of therapy in patients with PA onset before 21 years are suboptimal, despite aggressive therapy. Somatotropinomas are particularly resistant, partly due to *AIP* mutations.

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P852

Psychopathology in Cushing's disease and acromegaly

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Introduction

Cushing's disease (CD) and acromegaly, despite their different specific symptoms, often present psychopathology (mainly depression and anxiety) even after hormonal normalization. However, their psychopathological profiles may be different. The aim of this study was to analyse the psychopathological profile in successfully treated Acromegaly and CD, and to compare both diseases. Current hormonal evaluation and time since endocrine control will also be analysed.

Methods

Twenty-one patients in remission of CD, twenty patients with controlled acromegaly for at least one year and 41 matched controls for age, sex and education years were included in the study. They completed SCL-90R, Beck Depression Inventory II (BDI-II), State- Trait Anxiety Inventory (STAI) and underwent endocrine evaluation.

Results

Patients with CD and acromegaly presented more psychopathology than controls in most of the areas evaluated (Depression, Anxiety, Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Hostility, Paranoid Ideation, Psychoticism, Global Severity Index, Positive Symptom Distress Index and Positive Symptoms Total $P < 0.05$ all). No differences were found between CD patients and controls for Phobic Anxiety, or between acromegalic patients and controls for Paranoid Ideation and Phobic Anxiety. When comparing both patient groups, scores were similar for BDI-II, STAI and most of the areas of the SCL-90 questionnaire. Only for Somatization ($P < 0.001$), Paranoid Ideation ($P = 0.036$) and Global Severity Index ($P = 0.036$) CS patients had higher scores, while in acromegaly scores were higher for Positive Symptoms Total ($P = 0.001$). In CD (excluding those taking hydrocortisone), correlations were found between psychopathology and both morning cortisol (STAI-State: $P = 0.027$, $R = 0.521$, STAI-Trait: $P = 0.037$, $R = 0.495$, Depression $P = 0.035$, $R = 0.513$, Hostility: $P = 0.041$, $R = 0.500$) and 24 hour urinary free cortisol (STAI-Trait: $P = 0.038$, $R = 0.521$, Depression: $P = 0.038$, $R = 0.539$, Hostility: $P = 0.007$, $R = 0.663$, Psychoticism: $P = 0.024$, $R = 0.578$, Global Severity Index: $P = 0.012$, $R = 0.629$, Positive Symptoms Total: $P = 0.040$, $R = 0.534$). No correlations were found between psychopathology and IGF1 or GH in acromegaly. No correlations were found in normal controls between psychopathology and hormonal parameters. Psychopathology did not correlate with time since endocrine control.

Conclusions

After at least 1 year of cure, patients with CD and acromegaly score higher on psychopathology than controls. Current cortisol evaluation, despite being within normal values, correlated with psychopathology in CD, but not in controls. Despite some similarities, CD showed more somatizations, paranoid ideation and higher severity of psychopathological symptoms, while acromegalic patients reported a higher number of psychopathological symptoms.

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P853

Presence of empty sella in a patient with clinical and biochemical diagnosis of acromegaly

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Introduction
Acromegaly is an acquired disorder related to excessive production of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). It is characterized by progressive somatic disfigurement and systemic manifestations. Empty sella (ES) is an anatomical condition comprising sella turcica that is partially or completely filled with cerebrospinal fluid mainly due to intrasellar herniation of subarachnoid space. Primary ES may be associated with endocrine dysfunction and intracranial hypertension. Primary ES has to be distinguished from secondary ES, which has been linked to iatrogenic factors (surgery, radiation, medical treatment) or may be due to pituitary tumor apoplexy or autoimmune hypophysitis. Here, we describe a patient who presented with clinical and biochemical features of acromegaly and who had an empty sella on pituitary MRI.
Case
A 73-year-old male patient was consulted to our clinic for acromegalic phenotype while planning to be operated due to colorectal adenocarsinoma. The patient noticed gradual enlarging of his hands, feet, lips, and nose for 30 years, but never consulted to any clinician for this reason. Physical examination revealed typical acromegalic features. Visual field defect was not detected. Laboratory data showed elevated serum growth hormone (GH; 20.6 ng/ml)(normal <3 ng/ml) and insulin-like growth factor-1 (IGF-1; 531 ng/ml)(normal, 69–200 ng/ml). An oral glucose tolerance test (OGTT) showed no suppression of GH values. Serum levels of prolactin (PRL), adrenocorticotropic hormone (ACTH), cortisol (CS), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), andluteinizing hormone (LH) were normal. T1-weighted magnetic resonance imaging (MRI) revealed an empty sella. Thorax computed tomography (CT), abdomen CT and 18F-FDG PET-CT did not have any finding consisted with ectopic GH secretion. Adenoma releasing growth hormone releasing hormone (GHRH) was not considered as GHRH was in the normal range (<100 mg/dl).He was treated with Octreotide LAR 20 mg per 28 days. At 6th month evaluation, serum GH and IGF-1 levels were decreased to 5.45 ng/ml and 274 ng/ml (normal, 69–200 ng/ml), respectively.
Conclusion
The mechanism underlying the association of acromegaly and empty sella remains unclear. However, our patient did not have a history of pituitary apoplexy, we should keep in mind that apoplexy on existing pituitary adenoma and then formation of necrosis can proceed empty sella. Yet, we have not found any reason for secondary empty sella in our patient. So, he has probably primary empty sella.

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P854

The metabolic disturbances in acromegaly patients in relation to total, acylated and unacylated ghrelin

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Purpose
Acromegaly is a disease characterized by the excessive secretion of GH. Clinically, it is manifested by overgrowth of tissues and internal organs, which leads to characteristic phenotype. Patients with active acromegaly usually have impaired glucose metabolism. It significantly improves after achieving remission of the disease. Adversely, disturbances in lipid profile are not altering. Moreover, these parameters are even worse in successfully treated patients. Ghrelin strongly stimulates growth hormone secretion from anterior pituitary, as well as regulates the energy balance and various metabolic parameters. It is known that ghrelin affects glucose and lipid metabolism. It was shown that ghrelin level changes during treatment of acromegaly in earlier papers. Ghrelin occurs in acylated (AG) or unacylated (UG) form. Unacylated protein until recently was considered to be inactive. However, the latest research suggested that both forms may play biological functions. We aimed to evaluate the levels of total, acylated and unacylated ghrelin in medically naive and treated patients with biochemically active acromegaly in respect to variables of lipid and glucose metabolism.
Methods
The study group consisted of 24 patients diagnosed with active acromegaly. In study group nine patients were newly diagnosed and 16 patients received somatostatin analogs (9 lanreotide, 6 octreotide). Fifteen healthy volunteers served as controls. The physical examination of each subject was performed. Plasma levels of total ghrelin (TG), AG, calculated UG, GH, IGF1, insulin, glucose, total cholesterol, HDL cholesterol and calculated LDL cholesterol, triglycerides, apolipoproteins A-I (apoA-I) and B-100 (apo B-100) were measured.
Results
Total ghrelin levels in patients with acromegaly were decreased compared to healthy controls. In pooled data of all subgroups, simple linear regression analysis revealed that total ghrelin concentration was significantly associated with Apo-A1 concentration ($\beta=0.8087$; $P=0.0315$), and acylated ghrelin concentration was significantly associated with fasting insulin concentration ($\beta=15.5183$; $P=0.011$). We also observed an inverse association between unacylated ghrelin and patients' age, and its positive association with Apo-A1.
Conclusions
Ghrelin probably influences metabolic disturbances in acromegaly. We suggest to evaluate acylated and unacylated ghrelin in all patient. It seems to be probable that changes in ghrelin forms proportions are responsible for observed disturbances.

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P855

Hypopituitarism in primary empty sella

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Empty sella is characterized by the radiological appearance of an enlarged or deformed sella turcica which is completely or partially filled with cerebrospinal fluid resulting in a displacement of the normal pituitary gland. Primary empty sella (PES) refers to the empty sella appearance of unknown etiology, diagnosed after excluding a history of previous pituitary pathology. The prevalence of hypopituitarism in empty sella syndrome varies between 2 and 32% in different published series. The aim of this study was to investigate the incidence of hypopituitarism among PES patients. We conducted a retrospective analysis of the pituitary function in 46 consecutive patients (19 male, 27 female, median age 58 years (27–78)) with PES who were referred to the University Hospital Centre Zagreb between 2010 and 2016. Hypopituitarism was defined as the deficiency of one of the three hormonal axes (corticotroph, thyreotroph or gonadotroph). Hypopituitarism was present in 11 out of 46 PES patients (seven male, four female). Five patients had one pituitary axis insufficiency, four patients had two pituitary axis insufficiency and two patients had the insufficiency of all three pituitary axes. The insufficiency of the corticotroph, thyreotroph and gonadotroph axis was present in 17%, 17%, and 15% of patients, respectively. According to our results, every fourth patient with PES has at last one pituitary axis insufficiency. Therefore, in all PES patients regular endocrine work-up should be recommended.

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P856

A first-in-human pharmacokinetic, safety, and tolerability study of pasireotide subcutaneous depot

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Background
Pasireotide is available in twice-daily subcutaneous (sc) and long-acting intramuscular (im) formulations. Pasireotide sc depot is an investigational

extended-release sc formulation designed for improved handling and administration. Results are reported from a Phase I dose-escalating study.
Methods
All subjects received a single dose of pasireotide sc (600 μg) and were randomized 12:2:2 to pasireotide sc depot as a single upper-thigh injection (in five ascending-dose groups: 5, 10, 20 [another group of 12 subjects added at this dose level received a single buttock injection], 40, and 80 mg), long-acting pasireotide (60 mg), or pasireotide s.c. (900 μg) twice daily for 7 days.
Results
94 subjects (59 male, 35 female) were randomized; 90 (95.7%) completed the study. After pasireotide sc depot injection, pasireotide plasma profiles for all tested doses (5–80 mg) showed a relatively rapid initial release (median t_{max} 24–97 hours) followed by a slow decay with a half-life suitable for once-monthly dosing. Across the pasireotide sc depot dose range, AUC_{inf} increased dose proportionally and C_{max} slightly more than dose proportionally. AUC_{inf} and C_{max} for the 40 and 80 mg doses of pasireotide sc depot were within the exposure range for pasireotide im. Pasireotide pharmacokinetic parameters were comparable after buttock and upper-thigh injections of pasireotide sc depot (20 mg). The relative pasireotide bioavailability for pasireotide sc depot versus pasireotide im (60 mg) was 52–98% for the 5–40 mg doses, and 115% for the 80 mg dose. Mean values for maximum relative inhibition of insulin-like growth factor 1 versus baseline were similar for pasireotide sc depot 40 and 80 mg and pasireotide im 60 mg, but slightly lower for pasireotide sc depot 5, 10, and 20 mg. Overall, 76/94 (80.9%) subjects experienced adverse events (AEs). The incidence of AEs was 50%, 83.3%, 91.7%, 50%, 100%, and 100% for subjects in the 5, 10, 20 (upper thigh), 20 (buttock), 40, and 80 mg pasireotide sc depot dose groups, respectively, 100% for pasireotide sc, and 80% for pasireotide im. Diarrhoea (25/94 [26.6%]), injection-site pain (27/94 [28.7%]), and injection-site induration (21/94 [22.3%]) were the most commonly reported AEs. Most AEs were mild to moderate in intensity, with seven grade 3 AEs in five subjects (increased alanine aminotransferase [$n=3$], diarrhoea [$n=2$], increased gamma-glutamyl transferase [$n=1$], and vomiting [$n=1$]). There were no serious AEs, deaths, or AEs leading to discontinuation.
Conclusions
Pasireotide sc depot provides dose-proportional long-acting release of pasireotide with a safety and tolerability profile comparable to currently available long-acting im and sc formulations.

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P857

HLA celiac haplotypes and Primary Autoimmune Hypophysitis in Caucasian patients

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Purpose
Primary hypophysitis is a rare disease, with an autoimmune etiology. As few papers have investigated its genetic, our aim was to evaluate HLA status in a single-center series of patients.
Patients and method
A retrospective, longitudinal and cross-sectional study was conducted. Consecutive Caucasian patients, with clinical or histological diagnosis of primary autoimmune hypophysitis (PAH), undergone determination of HLA genotype, anti-pituitary and anti-hypothalamus auto-antibodies were included. This cohort was compared with a control group.
Results
A total of 16 patients was enrolled. Fourteen patients were female (87.5%). According to HLA-DR status, we found the following 9 out of 16 patients (56.3%) haplotypes that were associated to celiac disease (CD). Among these, 5 carried the DR7-DQ2 heterozygote haplotype (55.5%) while the remaining ones only the following haplotypes: DR3-DQ2 homozygote (25%), DR4-DQ2 heterozygote (25%), DR4-DQ8 heterozygote (50%), DR4-DQ8 homozygote (25%), respectively. A total of 12 CD-associated haplotypes were identified. In PAH, we found a significantly higher frequency of patients carrying CD-associated HLA-haplotypes as compared to the control group (respectively 75% vs 48% $P=0.03$; OR: 3.25 95%IC:1.1–10.3), particularly, for DQ2 and DQ8 haplotypes. DQ2 haplotype was detected in 50% of PAH and 38.4% of control group ($P=0.3$), while DQ8 haplotype in 25% of PAH and 7.2% of control group ($P=0.01$ OR:4.3 95%IC:1.3–14.7).
Conclusion
Our data suggest that PAH and CD share some HLA haplotypes, reinforcing the knowledge of their association. HLA haplotypes, particularly DQ8, may play a role in PAH management and diagnosis, also suggesting the predisposition to other autoimmune diseases.

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P858

Consensus on the management of acromegaly in Spain

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Objective
To find consensus on issues that may raise clinical doubts in the management of patients with acromegaly in Spain.
Methods
Nominal group and Delphi methodology was followed. Four experts on acromegaly were selected, who defined important clinical questions in the management of acromegaly. A set recommendations were proposed to solve these questions. Subsequently, a group of 30 additional endocrinologits from all over Spain was selected according to acromegaly expertise criteria. The level of agreement with the recommendations was tested through two Delphi rounds. A literature narrative review was performed in order to support the recommendations.
Results
The recommendations cover different aspects of clinical practice including: 1) Useful instruments for the individualization of treatment (predictive markers of treatment response, imaging techniques, etc.); 2) Specific clinical profiles of patients and relevant comorbidities for the individualization of the treatment; 3) Role of the patients in the treatment decision making; and 4) Access to treatments (accessibility and equity). In the first Delphi round, 35 recommendations were evaluated, reaching consensus in 6, 2 were eliminated and 2 reformulated. In the second Delphi round, 27 recommendations were included, reaching consensus in 24 (22 consensus in the agreement, 2 in the disagreement) and 3 were eliminated because they did not reach the level of agreement established. For example, consensus was reached to associate cabergoline in a partial response to 1st generation somatostatin analogs, before the use of other costly drugs. In the second line therapy, although the presence of a non-aggressive residual tumor mass following surgery does not contraindicate pegvisomant monotherapy, the experts consider that, if the residual tumor in close to the chiasm, pasireotide is the best choice. In addition, pasireotide may be indicated in case of partial tumor response with 1st generation somatostatin analogs. In diabetic patients with insufficient control, pegvisomant alone or associated with a 1st generation somatostatin analog is considered more adequate than pasireotide. However, diabetes is not considered a limiting factor for this treatment. On the other hand, the panel also consider that the acromegalic patients should be responsible for taking the treatment correctly, in order to obtain an adequate benefit. The same way, patients should have the possibility of a second opinion and to be treated in a reference center.
Conclusions
These recommendations aim to solve some common clinical questions and facilitate decision-making process in the management of patients with acromegaly in Spain.

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P859

PROMPT: a prospective study to assess efficacy and safety of metyrapone in endogenous Cushing's syndrome

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Introduction

Metyrapone blocks cortisol production by inhibiting 11ß-hydroxylation of 11-deoxycortisol, the last step of cortisol synthesis. Based on observational retrospective studies published over more than 50 years metyrapone is approved for the treatment of endogenous Cushing's syndrome (CS) in 14 European countries. PROMPT is the first prospective study to document the safety and efficacy of metyrapone using modern assay techniques.

Design and inclusion criteria

This is a single arm, open-label, multicenter, international trial. Adult patients with a new diagnosis of endogenous CS of any etiology (except advanced adrenal carcinoma) or recurrent or persistent Cushing's disease (CD) after transsphenoidal surgery (TSS), are eligible if three baseline 24 h Urinary Free Cortisol (UFC) values are at least 50% above the upper limit of normal (ULN = 165 nmol/24 h). Metyrapone given three or four times daily is titrated over 12 weeks to achieve normal urine and serum cortisol levels. After 12 weeks, patients whose mean value of 3 UFCs (mUFC) is less than 2-fold the ULN, may continue to receive metyrapone for another 24 weeks. Cortisol is measured in a central laboratory by LC-MS/MS.

Objectives

The primary objective is to assess the efficacy of metyrapone to normalise mUFC after 12 weeks of treatment. Secondary objectives are: assessment of the efficacy of metyrapone to normalise serum and salivary cortisol after 12 weeks and UFC after 24 weeks; assessment of changes in clinical symptoms of CS, blood pressure, quality of life (CushingQoL and Tuebingen CD QoL inventory); assessment of tolerance including adverse events and Ferriman-Gallwey score of hirsutism in women. The impact of metyrapone blockade on circulating lipids, glucose, ACTH, 11-deoxycortisol, deoxycorticosterone, renin/renin activity, androstenedione, DHEA-S and total testosterone levels is assessed. Time to 50% reduction of UFC, eucortisolemia, clinical and biochemical improvements, will be estimated. Exploratory objectives include factors predicting success and response relationships.

Status

The study started in 2015 and is ongoing in Belgium, Germany, Spain, Italy, Hungary, Poland and Turkey. To date 32 patients were included: 22 women and 10 men, with a mean age of 45 years old [21–73]; 29 have Cushing's disease (20 had previous TSS, range [1–3]). Fifteen completed the 9 months therapy period. Nine patients stopped study at/or after the primary objective endpoint: 2 for inefficacy, 1 because mUFC was >2xULN despite improvement by 70%, 1 for hirsutism, 1 for SAE (severe hypotension, cellulitis, venous thrombosis, and renal insufficiency) and 4 underwent TSS.

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P860

Mind the gap between cortisol levels measured with second generation assays and current diagnostic thresholds for the diagnosis of adrenal insufficiency: a single center experience

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Objective

The current cut-offs to diagnose adrenal insufficiency (AI) have been established using outdated immunoassays. More modern methods have demonstrated less cross-reactivity with other steroids. The aim of our study was to evaluate the correlation between the cortisol assay Roche Cortisol I (R1), the newly available Roche Cortisol II (R2) and liquid chromatography tandem mass spectrometry (LC-MS/MS), the gold standard procedure for the measurement of steroids.

Design

We enrolled 30 consecutive patients (age 47 ± 21 years) referred to our Center to undergo Synacthen test (1 or 250 µg). Blood samples were collected at 0, 30 and 60 minutes and cortisol was simultaneously measured with R1, R2 and LC-MS/MS. AI was diagnosed for R1 stimulated peak cortisol levels <18 µg/dl.

Results

Mean cortisol levels measured with R1, R2 and LC-MS/MS were respectively 14.9 ± 6.4, 10.4 ± 4.3 and 10.7 ± 4.3 µg/dl at basal conditions, 25.5 ± 7.4, 17.4 ± 4.8 and 18.1 ± 4.8 µg/dl at 30 minutes, 26.7 ± 10.9, 18.2 ± 7.1 and 18.8 ± 7.3 at 60 min after Synacthen test ($P \leq 0.01$ for R1 vs both R2 and LC-MS/MS; P = not significant for R2 vs LC-MS/MS at any time). Based on the correlation between R1 and R2 cortisol levels we calculated that the diagnostic threshold for AI would be 12.6 µg/dl if cortisol is measured with R2. Considering the 18 µg/dl cut-off AI was diagnosed in 5/30 patients using R1 and 12/30 using R2 (+140%).

Conclusions

The introduction of more specific cortisol assays results in lower cortisol levels and could lead to wrong diagnosis of AI. Cortisol levels by R2 method are similar to those found by LC-MS/MS. It could help clinician in the Synacthen test interpretation until new clinically-derived thresholds will be available.

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P861

An open-label, multicentre, single-arm, expanded-access study of subcutaneous (s.c.) pasireotide in patients with Cushing's disease (CD)

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Introduction

Pasireotide sc has a proven favourable efficacy and safety profile in CD patients, as shown in clinical trials. Here, we report safety and efficacy results from an expanded-access study designed to allow CD patients to receive pasireotide until regulatory approval for commercial use and reimbursement was obtained in their country.

Methods

Pasireotide-naïve adults with CD (mean 24-hour urinary free cortisol [mUFC; of three samples] exceeding the upper limit of normal [ULN]) were enrolled and initiated pasireotide sc at 600 µg bid (EU countries) or 900 µg bid (non-EU countries; 600 µg bid in patients with impaired glucose metabolism). Pasireotide dose could be increased/decreased in 300 µg increments/decrements to a maximum of 900 µg or a minimum of 300 µg for sustained UFC normalization/tolerability issues. The primary objective was to document the safety of pasireotide (primary endpoint: proportion of patients with a grade 3/4 or serious drug-related adverse event [AE]). Key secondary objectives included assessment of mUFC normalization and changes from baseline in clinical signs and quality of life (QoL) to weeks 12, 24 and 48.

Results

104 patients received pasireotide: female, $n = 84$ (80.8%); median duration of pasireotide exposure, 25.1 weeks; median (range) baseline UFC, 321.2 nmol/24h (142–10,920). Sixty-four (61.5%) patients discontinued treatment, most commonly for unsatisfactory therapeutic effect (25.0%), AEs (19.2%) and consent withdrawal (13.5%). Drug-related AEs occurred in 102 (98.1%) patients. Most AEs were mild/moderate severity; grade 3/4 drug-related AEs or serious AEs were documented in 42 (40.4%) patients, primarily metabolism/nutrition ($n = 20$; 19.2%) and gastrointestinal ($n = 13$; 12.5%) disorders. Most common grade 3/4 drug-related AEs were diabetes mellitus (10.6%) and hyperglycaemia (7.7%). At weeks 12, 24 and 48, respectively, 36/66 (54.5%), 22/46 (47.8%) and 9/21 (42.9%) evaluable patients had mUFC ≤ ULN. Improvements were observed in clinical signs; mean percentage change from baseline to week 48 in weight and sitting systolic and diastolic blood pressure was –7.0% (95%CI –9.1, –5.0), –4.9% (95%CI –7.9, –1.9) and –3.8% (95%CI –7.3, –0.4), respectively. Patients experienced a favourable shift in clinical signs and QoL improvement; mean CushingQoL scores increased by 34.4% (95%CI 19.5, 49.4) from baseline to week 48.

Conclusions
This study demonstrates that pasireotide is generally well tolerated, effectively reduces UFC (normalization in ~50% of evaluable patients) and improves clinical signs and QoL of CD patients in a setting similar to 'real-world' clinical practice. AEs were frequent but manageable for most patients, with <20% discontinuing because of AEs.

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P862

Growth hormone secretion in children treated for medulloblastoma

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Medulloblastoma is the most common malignant brain tumor in childhood. Treatment of medulloblastoma includes surgery, radiation therapy and chemotherapy. Craniospinal radiation can cause adverse effects on the endocrine system, specifically on the hypothalamic-pituitary axis. Increasing survival rates of pediatric patients with brain tumors lead to increased concern regarding long-term quality of life, including the detection and correction of endocrine disorders. One of the most frequent signs of endocrine dysfunction is growth and/or growth velocity retardation. We present data of growth hormone secretion in 28 patients with medulloblastoma after combined treatment (including craniospinal radiation). There were 20 boys (71.4%) and eight girls (28.6%). The mean age at time of examination was 10.2±2.75 yrs (6.2–15.5) The mean age of disease onset was 6.4±2.8 yrs (ranged from 1.1 to 13 yrs) and the time from end of therapy to our examination was 4.36±2.43 (0.5–13.4) yrs. Height SDS at the moment of examination (adjusted to age and sex) was −1.25±0.9 (−3.35 ÷ 0,21). Growth velocity did not exceed 2.5–3 cm/year in most patients. Growth hormone secretion was assessed by GH-stimulation test (clonidine or insulin). Total growth hormone deficiency was observed in 26/28 patients (92.9%), another two patients had partial GH-deficiency. Mean IGF-1 S.D.S. level (adjusted for sex, age and Tanner stage) was −1.35±0.9 (−5.2 ÷ 1.22), nevertheless 64.28% of patients (18/28) had normal IGF-1 level (i.e. IGF-1 SDS level from +1.2 to −2).
Conclusion
In the group of children, treated for medulloblastoma (including craniospinal therapy) we received growth hormone deficiency (total or partial) in 100% of patients, whereas 64.28% of them had normal IGF-1 level. We conclude that all patients with a history of craniospinal radiation should be screened for growth hormone deficiency. IGF-1 level cannot serve as a sensitive additional marker in this case.

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P863

Interim results of a non-interventional, observational study evaluating the long-term safety and efficacy of pasireotide sc in Cushing's disease

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Introduction
Subcutaneous (sc) pasireotide effectively reduces cortisol levels, improves signs/symptoms and is generally well tolerated in Cushing's disease (CD) patients, as shown in previous clinical trials. We report interim results from a multicentre, real-world observational study evaluating the long-term safety and efficacy of pasireotide sc in clinical practice in CD patients.
Methods
Adults with CD, for whom surgery has failed or is not an option, are being enrolled. Primary objective: document the long-term (3-year follow-up) safety and tolerability of pasireotide. Secondary objective: document the short- and long-term efficacy of pasireotide as measured by the proportion of patients achieving mean urinary free cortisol (mUFC) below the upper limit of normal (ULN) at months 1, 3, 6, 12, 24 and 36. Patients are grouped by whether pasireotide was started before (prior-use) or at (new-use) study entry.
Results
As of 1 October 2016, 99 patients have been recruited and received ≥1 pasireotide dose after enrolment: 78 prior-use (mean time from diagnosis, 81.3 months; female, 80.8%) and 21 new-use (mean time from diagnosis, 40.7 months; female, 66.7%). Median (range) exposure to pasireotide: prior-use, 7.2 months (0.1–36.3) on study, 25.3 months (2.0–108.5) from drug initiation; new-use, 2.9 months (0.1–12.1) on study. Eighty-nine (prior-use, $n=69$; new-use, $n=20$) patients had ≥1 safety assessment after enrolment, of whom 65 (73.0%) experienced ≥1 adverse event (AE). Forty-three patients (48.3%) had ≥1 drug-related AE, most commonly nausea (prior-use, $n=6$ (8.7%); new-use, $n=7$ (35.0%)), diarrhoea (prior-use, $n=5$ (7.2%); new-use, $n=3$ (15.0%)) and hyperglycaemia (prior-use, $n=3$ (4.3%); new-use, $n=5$ (25.0%)). Drug-related serious AEs were documented in 8/69 prior-use (11.6%; hyperglycaemia, $n=1$ (1.4%)) and 4/20 new-use (20.0%; hyperglycaemia, $n=3$ (15.0%)) patients. Of patients with a normal/pre-diabetic HbA_{1c} level at baseline, 3/15 (20.0%) prior-use and 4/6 (66.7%) new-use patients had a highest-reported level in the diabetic range during the study. Of evaluable patients in the prior-use and new-use groups, respectively, mUFC was ≤ULN in 23/34 (67.6%) and 1/10 (10.0%) patients at baseline, 9/16 (56.3%) and 7/14 (50.0%) at month 1, 18/22 (81.8%) and 1/3 (33.3%) at month 6, and 16/18 (88.9%) and 0/0 at month 12.
Conclusions
Results from this study demonstrate the favourable risk/benefit profile of pasireotide sc in CD patients, confirming findings from previous clinical trials. The lower incidence of hyperglycaemia in prior-use versus new-use patients indicates that glycaemic control does not deteriorate over time, which is potentially attributable to appropriate management at its onset.

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P864

An immunohistochemical study on pituitary adenomas

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Introduction
Pituitary adenomas (PA) represent approximately 15% of all intracranial neoplasms, with a global incidence of 15,20 per million per year. The immunohistochemical analysis of PA is necessary for diagnosis and plays an important role in the modern classification system of pituitary tumors.
Material and methods
Samples from 142 surgically resected PA were studied immunohistochemically using antisera for 6 anterior pituitary hormones. Reticulin fiber staining and routine hematoxylin-eosin staining were also used. There were 57 patients with acromegaly (ACM), 29 prolactinomas (PRM), 55 non-functioning PA (NFPA) and 1 PA with mixed secretion of growth-hormone (GH) and prolactin (PRL).
Results
Immunohistochemical staining was positive for one hormone in 44% cases, 34% staining positive for multiple hormones. 21% of tumors failed to stain for any of the main pituitary hormones (null-cell adenomas). Most PA were acidophilic (105/142), the rest being basophilic (14/142), chromophobe (7/142) or mixed (16/142). In patients with ACM, most tumors were GH- (54%), mixed GH and PRL-producing (23%) and plurihormonal PA (9%). In the other cases (14%) the immunostaining results were discordant with the clinicobiological data. Prolactinomas were 75% PRL-producing PA, the rest being mixed GH and PRL or plurihormonal (7% each); discordant results were obtained in 11%. In our study, 32/55 (58%) of NFPA showed hormonal immunoreactivity: 13.5% (5/37) for GH, 89% (16/18) for FSH/LH, 6/13 (46%) plurihormonal PA and 11% (2/18) mixed GH-PRL. TSH, PRL and ACTH exclusive immunoreactivity were found each in one case. Most tumors immunopositive for GH (28/37), GH and PRL (13/18) and plurihormonal (8/13) were positive for reticulin, while those positive for PRL (9/23), ACTH (1/2), FSH-LH (7/18) and null-cell adenomas (14/30) stained less for reticulin. The only TSH-producing adenoma in the study stained negative for reticulin.
Conclusion
The immunohistochemical characterization of PA is useful for an accurate diagnosis. However, the hormonal immunoreactivity of these tumors is not always correlated with the synthesis and the release rate of the hormones. That is why the revised classification of pituitary adenomas (WHO, 2017) recognizes the role of many other immunohistochemical markers and transcription factors. Their widespread use will hopefully aid in the early identification of aggressive pituitary adenomas and in improving management strategies.

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P865

Inferior petrosal or cavernous sinus sampling in ACTH-dependent Cushing's syndrome: a single center experience

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Objective
Most patients with ACTH-dependent Cushing's syndrome have Cushing's disease, i.e. a pituitary corticotroph adenoma, but the presence of another tumor secreting ACTH (although the prevalence of ectopic ACTH syndrome is lower) needs to be considered in the differential diagnosis. Distinguishing between these two etiologies can be difficult despite biochemical and radiological examinations. Previous research showed that inferior petrosal/cavernous sinus sampling (IPSS/CSS) has the highest diagnostic accuracy in this differential diagnosis. The aim of this study was to determine the accuracy of IPSS/CSS in predicting the source of ACTH-dependent Cushing syndrome in a tertiary center in Switzerland.
Methods
Retrospective, single center study of 21 patients (seven male, 14 female; age 40.4 ± 16.8y) with ACTH-dependent Cushing's syndrome who underwent a selective bilateral inferior petrosal sinus ($n=6$) or superselective bilateral cavernous sinus ($n=15$) sampling at the University Hospital Zurich between 2000 and 2017 and provided written informed consent. ACTH levels were measured before and within 20 min after corticotropin-releasing hormone (CRH) administration, and the ratios of central-to-peripheral plus interpetrosal ACTH levels were calculated. A central-to-peripheral ratio ≥ 2 before and ≥ 3 after CRH is diagnostic of an orthotopic source of ACTH. A ratio ≥ 1.4 between the two sinuses predicted the tumor lateralization.
Results
IPSS/CSS confirmed orthotopic (pituitary) source of ACTH in 19 patients with Cushing's disease and correctly identified 2 patients with ectopic disease. A central-to-peripheral plasma ACTH ratio was diagnostic for Cushing's disease in 19 patients before CRH and in 19 patients after CRH-administration. Interpetrosal ratios for ACTH lateralization were found in 17 (pre-CRH) and 17 (post-CRH) patients. The IPSS/CSS pre- and post-CRH ACTH ratio was negative (close to 1) in both patients with ectopic Cushing's syndrome. There was no adverse event in the context of the catheterization procedure. Perioperative MRI ($n=18$) showed 1 macroadenoma, 12 microadenomas and no visible lesion in five patients. In patients with visible pituitary lesions, IPSS/CSS predicted correctly the localization to the left, right or paramedian side in seven cases. Judged by surgery, the IPSS/CSS predicted correctly the lateralization of the pituitary tumor in 14 of 19 patients. Pituitary surgery was successful in 14 patients; five had persistent cortisol excess.
Conclusion
Our results confirm previous reports that IPSS/CSS is an effective intervention to locate the source of ACTH production. IPSS/CSS was safe and useful in planning the surgical therapy in patients with Cushing disease.

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P866

Relationship between pituitary adenoma size and transsphenoidal pituitary adenoma surgery outcomes: single-centre experience

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Introduction
Stereotactic radiotherapy and more relevant pharmacotherapy are widely used for PA's treatment; however transsphenoidal surgery remains gold standard. Postoperative complications and endocrinological outcomes vary widely and are related with surgeon experience and tumor characteristics.
The aim of this study
To determine relationship between pituitary adenoma size and transsphenoidal pituitary adenoma surgery outcomes.
Materials and methods
We performed a retrospective analysis of medical records for patients with pituitary tumor, who underwent transsphenoidal pituitary surgery during 2007–2016 year period at the Hospital of Lithuanian University of Health Sciences Kauno Klinikos. Data consisted of 217 patients: 121 (55.76%) male and 96 (44.24%) female, with a mean age of 52.84 ± 15.70 yrs (range 18–84 yrs). Relationship between tumor size, postoperative complications and endocrinological outcomes has been evaluated. The difference between proportions was confirmed using the χ^2 criterion. The odds ratio was calculated using 2×2 table methodic. Results were interpreted as statistically significant when $P<0.05$.
Results
The study included 123 nonfunctioning and 94 functioning adenomas: 38 were prolactinomas, 12 growth hormone (GH) and four corticotropin (ACTH) secreting adenomas. The majority of tumors 174 (80.18%) were macro adenomas (>1 cm), 26 (11.99%) micro adenomas (<1 cm) and 18 (8.29%) giant adenomas (>4 cm). The most common presenting symptoms were visual disturbance 117 (53.91%) and headache 122 (56.22%). Possibility for visual disturbance before surgery was significantly higher in macro adenomas group (OR 1.89 (±95 CI 1.66–2.17); $P=0.038$). Hypopituitarism prior operation was reported for 7 (3.22%) patients, all presented with nonfunctioning macro adenomas. Postoperative complications were observed in 31 (14.28%) patients. We confirmed that after surgery in patients with macro adenomas visual field (VF) and visual acuity (VA) improvement chance was significantly higher (VF OR 2.28 (±95 CI 1.12–1.46); $P=0.03$), (VA OR 2.15 (±95 CI 1.89–2.46); $P=0.03$). Odds to have the same VF and VA parameters after micro adenomas surgery were the following: VF OR 1.28 (±95 CI 1.13–1.47); $P=0.03$), VA OR 2.40 (±95 CI 2.1–2.74); $P=0.03$. After surgery remission achieved for 81 (37.32%) patients. Hypopituitarism was observed in 21 (8.42) patients and risk was significantly higher after macro adenomas surgery (OR 1.25 (±95 CI 1.1–1.44); $P=0.05$).
Conclusions
Our study demonstrated significant improvement of VF and VA, but higher risk for postoperative hypopituitarism after pituitary macro adenomas trassphenoidal surgery.

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P867

Clinical and mri findings among 120 patients with macroprolactinemia: results from a retrospective study

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Background
Macroprolactinemia is a condition where more of 60% of circulating PRL is made up of macroprolactin. It may be observed in both sexes (although women represent about 90% of published cases), and at all ages. As macroprolactin has low biological active and low bioavailibility, most patients are asymptomatic. The Endocrine Society guidelines recommend screening for macroprolactin only in asymptomatic hyperprolactinemic patients. However, some data from the literature have challenged this recommendation.
Subjects and methods
The aim of this retrospective study was to evaluate clinical presentation and MRI findings among 220 patients with macroprolactinemia routinely followed at Division of Endocrinology, Hospital das Clinicas, Federal University of Pernambuco, and at Pernambuco Endocrine Research Center, Recife, Brazil.
Results
A total of 120 patients (100 women and 20 men; mean age, 32.5 ± 6.5 yrs; age range, 19–46) were included. The great majority of female patients had been referred by gynecologists. Overall, 69 patients (57.5%) were asymptomatic, whereas 51 (42.5%) presented with symptoms related to hyperprolactinemia. Among the 100 female patients, 13% had galactorrhea, 26% menstrual disorders, and 3% both, whereas 58% were asymptomatic. Among the 20 male patients, 5 (30%) had erectile dysfunction, 3 (15%) had decreased libido and 1 (5%) both, whereas 11 (55%) subjects were asymptomatic. Abnormal MRI findings were found in 28 patients (23.3%): microadenomas in 16 (13.3%), empty sella in 8 (6.7%), and macroadenomas in 4 (3.3%).
Conclusion
Our findings demonstrated that abnormal MRI findings and particularly symptoms related to hyperprolactinemia are frequent features in patients with macroprolactinemia. Therefore, screening for macroprolactin only in asymptomatic patients seems to be an inappropriate approach.

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P868

Hypothalamic-pituitary axis assessment in a clozapine treated patient with a pituitary adenoma

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Background
Assessment of hypothalamic–pituitary adrenal axis in patients with schizophrenia is complex, as it involves both the disease process and antipsychotic medications. We present a case of a patient on long term clozapine with a concomitant pituitary adenoma who presented discordant responses to adrenal stimulation.
Case
A 38-year old male was referred with chronic symptoms of reduced libido and associated low testosterone levels. He was treated for paranoid schizophrenia with clozapine 100 mg q.am and 400 mg note for many years. On further assessment he was normally masculinized, with testes of normal size and texture and no galactorrhea. However, testosterone levels were confirmed low at 20 mg/dl with low gonadotropins (FSH 1.51 mIU/ml, LH 0.73 mIU/ml), normal prolactin 7.93 ng/ml, TSH 2.52 μIU/ml and fT_4 0.68 ng/dl (normal 0.84–1.76). IGF-1 and morning cortisol levels were frankly low, at 26 ng/ml (normal range for age and sex 94–360) and 3.44 μg/dl respectively, making the diagnosis of panhypopituitarism. MRI of the sella showed a pituitary adenoma 10×10.7 mm. He was placed on hydrocortisone, thyroxine and testosterone replacement and underwent a successful endoscopic transphenoidal adenomectomy six months later. Stimulation with 1 μg tetracosactrin six months postoperatively showed a peak cortisol response of 11.7 μg/dl. Glucagon stimulation test also showed an inadequate peak cortisol response (9.32 μg/dl at 180′). At the same time, the responses of ACTH and cortisol to corticotropin-releasing hormone stimulation were normal, with a peak of 132 pg/ml at 15′ and 19.90 μg/dl at 30′ respectively. One year after surgery, morning cortisol levels were restored and hydrocortisone replacement was stopped. Repeat stimulation with 1 and 250 μg tetracosactrin and 1mg glucagon, showed peak cortisol responses of 16.0 at 30′, 21.60 at 60′ and 20.5 μg/dl at 180′, respectively. The patient remains GH, gonadotropin and TSH deficient.
Conclusions
1) Clozapine may blunt glucagon-stimulated ACTH secretion
2) Currently employed dynamic tests of adrenal axis in patients with pituitary pathology in the presence of antipsychotic medications cannot accurately reflect true capacity for stress response).

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P869

Comorbidities and symptoms among patients with acromegaly in italy: a longitudinal retrospective chart review study

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Acromegaly is a disorder characterized by overproduction of growth hormones (GH), which causes tissue growth in the body and comorbidities and symptoms. While prior studies examined comorbidities commonly associated with acromegaly, few have long follow-up periods necessary to characterize the long-term comorbidity profile of patients with acromegaly. There is limited literature on real-world treatment patterns of patients with acromegaly. This study describes the long-term prevalence of comorbidities and symptoms associated with acromegaly, as well as treatment patterns, in a major referral center in Italy. Medical records of adult patients with a confirmed acromegaly diagnosis, ≥2 valid readings of GH and IGF1, and ≥6 months of follow-up at the endocrinology center at the University Federico II in Naples, Italy, were reviewed. For this analysis, patients were followed from the 1st acromegaly diagnosis recorded by this study center until end of data availability, loss to follow-up, or death; some patients may have had an earlier diagnosis before referral to this center. Prevalence (i.e., ≥1 diagnosis during chart review period) of selected comorbidities and symptoms was described. Treatments with corresponding line of therapy was documented during the follow-up period. 150 patients met the eligibility criteria. Patients were on average 43.1 years old (range: 19–70) at diagnosis, 47.3% female, all Caucasian, and median follow-up time was 8.7 years (range: 0.8–35.5). 25.3% of patients had ≥15 years of follow-up. The 3 most prevalent comorbidities were 1) endocrine and metabolic system disorders (97.3% of patients), 2) cardiovascular system disorders ([CVsD], 76.0%) and 3) arthropathy (62.0%). Common endocrine and metabolic system component conditions included dyslipidemia (74.7%), nodular thyroid disease (72.3%), glucose metabolism abnormalities (50.0%), gonadal and menstrual disorders (50.0%) and obesity (40.7%). CVsD's component conditions included hypertension (59.3%), myocardial hypertrophy (50.0%) and other various CVsD's (45.5%). Cancer, cerebrovascular disease, colon polyps, metabolic syndrome and sleep apnea were reported in $<50\%$ of patients. 68.0% of patients underwent transphenoidal surgery during the chart review period. 85.3% of patients received somatostatin analogs (e.g., lanreotide [58.7%] and octreotide (54.0%)) at various treatment phases. Dopamine agonists were used by 34.0% of patients, mostly in 2nd, 3rd or 4th line of therapy. Pegvisomant was used by 30.0% of patients, mostly in 2nd or 3rd line of therapy. While these comorbidities and symptoms have been shown to be associated with acromegaly, this study provides further insight on their lifetime prevalence. Heterogeneity in the treatment patterns underscores real-world differences in patient management following diagnosis.

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P870

Safety and efficacy of long-acting Pasireotide monotherapy in acromegalic patients treated with a combination of first-generation somatostatin analogs and cabergoline or pegvisomant

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Introduction
Combination therapy using pegvisomant and cabergoline with first-generation long-acting somatostatin analogs (1GSSA) is a common procedure in acromegalic patients that are not fully controlled by surgery and 1GSSA. Pasireotide-LAR is a new multireceptor-targeted somatostatin receptor ligand that has superior efficacy over octreotide LAR to control GH and IGF1 levels. Little data is available about the efficacy and safety of pasireotide monotherapy in patients treated with a combination therapy.
Materiel and methods
Fourteen acromegalic patients (10 women, aged: 47 ± 11 y) treated with octreotide LAR (30 mg/Mo, $N=8$) or lanreotide SR (120 mg/Mo, $N=6$), and cabergoline ($N=4$, weekly dose $=3.5$ mg) or pegvisomant ($N=10$, weekly dose 40–200 mg) were prospectively enrolled in an open study and switched to pasireotide-LAR monotherapy (half with 40 mg and half with 60 mg/Mo). Seven patients already had diabetes mellitus, two patients had glucose intolerance. Clinical, biological and radiological evaluations were performed before (baseline), 3 months after the switch and at 6 Mo or later.
Results
IGF1 level at 3 Mo and baseline were similar (median $=1.1$ vs 1.1 ULN). Median GH was 1.54 ng/ml (min $=0.14$-max $=8.9$). As compared to baseline, six patients vs five had IGF1 below 1ULN. A significant increase in fasting blood glucose and HbA1c was observed at 3 Mo vs baseline: 1.15 g/l (0.82–1.6) vs 1.02 (0.9–1.78) ($P=0.05$) and 6.4% (5.4–8.4) vs 5.7% (5.3–7.2) ($P=0.002$) respectively. A new anti-diabetic treatment was initiated in six patients (including five with diabetes at baseline). During the follow-up, six patients stopped Pasireotide-LAR for lack of control of IGF-1 ($N=2$), intolerance despite control (dizziness $N=1$ and hyperglycemia $N=1$), and lack of control associated with hyperglycemia ($N=2$). Eight patients were treated with Pasireotide-LAR for a median duration of 8 months (2–17) with a controlled IGF1 (0.5–1.1 ULN) and acceptable glucose tolerance (median HbA1c 6.1% (5.4–7.4)). Three of these 8 patients required antidiabetic treatment intensification (increase in insulin dosage in 1) or initiation (oral antidiabetic treatments in two). Five patients had normal glucose tolerance without pharmacological treatment.
Conclusion
In this small series, Pasireotide-LAR is an efficient alternative with acceptable tolerance in a subset of acromegalic patients treated with a combination therapy involving 1GSSA.

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P871

Association between biochemical control and comorbidities and symptoms among patients with acromegaly in Italy: a longitudinal retrospective chart review study

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Acromegaly is a rare disorder characterized by the overproduction of growth hormone (GH) and elevated insulin-like growth factor-1 (IGF1). While some studies have investigated the potential associations between biochemical control (i.e., normalization of IGF-1 and/or GH) and comorbidities/symptoms, few studies have long-term follow-up. This study assessed the association between biochemical control and selected comorbidities/symptoms in patients with acromegaly using real world longitudinal data. Medical records of adult patients with a confirmed acromegaly diagnosis, $\geq$2 valid readings of GH and IGF1, and $\geq$6 months of follow-up at an endocrinology center in Naples, Italy, were reviewed. For this analysis, patients were followed from the first medical encounter with a GH/IGF1 measurement at the center until the occurrence of comorbidities/symptoms (i.e., event), loss to follow-up, or death (i.e., censoring). Biochemical control was assessed annually and defined as having $>$50% days with IGF1 measurements $\leq$ the upper limit of normal, or GH measurements $\geq$2.5 µg/l when IGF1 was not available. Comorbidities/symptoms assessed included arthropathy, cancer, cardiovascular system disorders (CVsD) and component conditions, cerebrovascular disease, colon polyps, endocrine and metabolic system disorders and component conditions, and sleep apnea. Time-varying Cox models, adjusting for age and sex, were used to assess the association between biochemical control and comorbidities/symptoms. Hazard ratios (HRs) and confidence intervals (CIs) were estimated. Of the 150 eligible patients, all were Caucasian, 47% were female, on average 43.1 years old (range: 19–70) at diagnosis, with a mean follow-up time of 8 years (range: 0–31). The mean GH level during the follow-up was 8.3$\pm$11.9 µg/l and 367.7$\pm$154.2 µg/ml for IGF1. The three most commonly observed incident comorbidities/symptoms during follow-up were endocrine and metabolic system disorders (94.3%), CVsD (63.4%), and arthropathy (48.5%). Biochemical control was significantly associated with a lower hazard of CVsD (HR=0.54, 95% CI=0.31–0.93). While significance was not reached for endocrine and metabolic system disorders as a whole (HR=1.01, 95% CI=0.78–1.33), biochemical control was significantly associated with a lower hazard of diabetes (HR=0.36, 95% CI=0.15–0.83). Biochemical control was significantly associated with a higher hazard of certain types of arthropathy (HR=1.68, 95% CI=1.04–2.71), but not with the remaining comorbidities/symptoms assessed. These results highlight the importance of achieving biochemical control, since this may reduce the risk of costly conditions, including CVsD and diabetes. The association found for arthropathy may suggest the irreversibility of this acromegaly-related impairment.

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P872

Trends of insulin-like growth factor 1, growth hormone, and biochemical control of patients with acromegaly in italy: a longitudinal retrospective chart review study

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Long-term biochemical control (i.e., normalization of growth hormone [GH] and insulin-like growth factor-1 [IGF1]) is the goal of treatment of acromegaly. Few studies have characterized the sustainability of GH/IGF1 levels in acromegaly patients. This study aimed to identify long-term time trends of GH, IGF1 levels, and biochemical control in patients with acromegaly using longitudinal real world data. Medical records of adult patients with a confirmed acromegaly diagnosis, $\geq$2 readings of GH and IGF1, and $\geq$6 months of follow-up at an endocrinology center in Italy, were reviewed. Patients were followed from first documented GH and/or IGF1 measurement at the study center until end of data availability, loss to follow-up, or death. Mean GH and IGF1 levels were obtained across multiple measurements per year. Biochemical control was assessed annually and defined as having $>$50% of IGF1 measurements $\leq$upper limit of normal, or GH measurements $\leq$2.5 µg/L (when IGF1 unavailable). Latent class growth analyses were conducted to identify different time trends of mean IGF1, mean GH, and probability of being biochemically controlled over 10 years, and to estimate the proportion of patients presenting with these time trends. Trend assignments were based on model fit. All 150 eligible patients were Caucasian, 47% female, with mean age of 43.1 years (range: 19–70) at diagnosis and a mean follow-up time of 9 years. 81 (54%), 84 (57%), and 81 (54%) patients had normal IGF1, GH, and biochemical control status, respectively, for $\geq$50% of the follow-up period. Four trends were identified for IGF1 (% of population; mean levels): one stable (15.3%; 186.5 ng/mL) and three declining ([1] 39.3%; initial [year 1]: 465.8, last [year 10]: 142.9; [2] 38.0%; initial: 576.8, last: 280.1; [3] 7.3% initial: 664.1, last: 403.4). Three declining trends were identified for GH ([1] 23.6%; initial: 1.63 µg/L, last: 0.32 µg/L; [2] 50.7%; initial: 4.57, last: 1.03; [3] 25.7% initial: 12.99, last: 3.34). Probability of achieving biochemical control followed two trends (% of the population; probability of control): one stable (26.7%; 20.4%) and one increasing (73.3%; initial: 33.1%, last: 98.0%). Results show that IGF1 and GH levels were initially elevated in the majority of patients, and declined over time. Biochemical control was reached by $\geq$70% of patients after 10 years. One-third of the population had low likelihood of achieving control at any time. Future research is warranted to understand the impact of long-term biochemical levels on patients' disease course.

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P873

Pituitary intensity at magnetic resonance imaging is reduced in obese patients: results from the CHIASM study

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Introduction
Even if obesity has been associated to several hormonal imbalances, pituitary appearance at Magnetic Resonance Imaging (MRI) in obese patients is understudied.
Aim
To measure pituitary signal intensity and homogeneity at MRI in obese subjects free of focal pituitary disease, in the context of the CHIasM study (Changes in the Hypotalamic-pItuitary region of patients with Metabolic syndrome and obesity).
Materials and methods
Seventy-eight patients were prospectively enrolled and underwent metabolic, hormonal, body composition (DEXA scan) and pituitary MR assessment. Patients were divided in two groups according to BMI (study group $\geq$ 30 kg/m^2, 55 patients, control group $<$ 30 kg/m^2, 23 patients). Texture of the pituitary gland was quantified recording pixel density and distribution using ImageJ software. Two operators independently placed the region of interest to entirely cover the pituitary gland, calculating mean intensity and its standard deviation. All analyses were normalized for both white and grey brain matter intensity.
Results
In the study group, we demonstrated a statistically significant reduction in mean pituitary intensity in T1 weighted images both in basal (P=0.038) and contrast-enhanced sequences (P=0.002), trough analysis of covariance (ANCOVA). Moreover, pituitary intensity in T1-weighted basal and contrast-enhanced images was negatively correlated to truncal fat (P 0.008, P 0.011) and fibrinogen (P=0.011, P=0.005). Multiple regression analysis revealed that, after adjusting for age and sex, the percentage of truncal fat and fibrinogen were significant predictors of the mean intensity of coronal T1-weighted scans (P=0.001). The model explained up to 26% of variance of pituitary signal intensity, and in a step-wise R^2 analysis fibrinogen itself accounted for 9.6% of the variance.
Conclusions
This study describes a quantitative reduction in pituitary intensity in T1-weighted sequences in obese patients, that seems related to visceral adiposity and low-grade inflammation. Data could be explained by a relative change in pituitary stromal tissue in this cohort of patients.

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P874

The influence of levothyroxine (T4) treatment on metabolic parameters in central hypothyroidism (CH)

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Introduction
L thyroxin treatment of CH is monitored by free T4 (fT4) which should be above mid normal range for the assay. It is not clear whether these doses are adequate for regulating the metabolic disturbances accompanying CH.
Aim
To determine whether T4 therapy leads to improvement of metabolic parameters in CH.
Materials and methods
This was a retrospective study. Study group comprised of 60 hypopituitary patients with CH, controls were 18 patients with hypopituitarism without CH. We analyzed fT4 and freeT3 (fT3), daily T4 dose, duration of CH, number of pituitary deficits, body mass index (BMI), arterial blood pressure, total cholesterol (TC), triglycerides, HDL, LDL, fasting blood glucose (FBG) and insulinemia, HOMA IR, and spine and hip bone mineral density (BMD).
Results
fT4 was normal in both groups (13.55 ± 2.72 vs. 13.54 ± 1.86 pmol/l). FT3 was normal but significantly lower in CH group (3.76 ± 0.84 vs. 4.45 ± 1.16 pmol/l; $P < 0.028$). Average dose of T4 was 1.26 ± 0.54 µg/kg/body weight. Duration of CH was 10.36 ± 11.69 years. Number of pituitary deficits was significantly higher in CH group ($P < 0.001$). Triglycerides were elevated in the CH group, but the difference was insignificant (1.91 ± 1.07 vs. $1.45 \pm 1.45 \pm 0.86$ mmol/l, $P = 0.10$). HDL was low in CH group and difference was significant (1.07 ± 0.32 vs. 1.52 ± 0.54, $P < 0.001$). Other parameters were normal and did not differ. FT4 was significantly positively correlated with HDL and negatively with hip BMD ($P < 0.05$; $P < 0.01$; $P < 0.002$). FT3 was significantly negatively correlated with FBG ($P < 0.02$). T4 dose was significantly positively correlated with BMI, negatively with spine and hip BMD ($P < 0.04$; $P < 0.008$; $P < 0.004$; $P < 0.007$). Duration of CH was significantly negatively correlated with spine and hip BMD ($P < 0.03$; $P < 0.004$; $P < 0.001$).
Conclusion
Apart from fT4 metabolic parameters should be taken into account when treating CH.

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P875

Efficacy of pasireotide lar in first line somatostatin analogue resistant acromegaly patients: experience from a large and single centre Italian cohort

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Introduction
Pasireotide Lar is a new generation long-acting somatostatin multireceptor ligand, approved for the treatment of first line somatostatin analogue resistant patients. We aimed to review Pasireotide Lar efficacy data, in our series of patients affected by aggressive acromegaly.
Patients
A retrospective longitudinal study was conducted on patients with aggressive acromegaly, resistant to first-line somatostatin analogues (SSA) and on treatment with Pasireotide Lar for at least 6 months. Clinical and radiological data at baseline (Pasireotide Lar start) and at follow-up were collected.
Results
Thirty-one patients met the inclusion criteria. 21 patients were treated with Pasireotide Lar during CSOM230C2304 clinical trial, 3 patients started treatment as for compassionate use and 7 patients started treatment after Pasireotide Lar marketing. 20 patients were female. Mean age at Pasireotide Lar start was 42 years (SD:11.6). All patients were considered affected by active acromegaly at Pasireotide Lar treatment start (mean GH:24.5 ng/mL SD: 46.7; mean IGF-I: 3.58 xUNL SD:1.77). All patients had undergone previous pituitary neurosurgery for macroadenoma and at baseline carried residual disease with cavernous sinus invasion. Ki67 was higher than 1.5% in all patients (mean:2.5 SD:1.7). Types IIa and V Somatostatin analogues receptors (SSTRs) immunohistochemical study was available in 11 patients. Particularly we found a high (score 3) immunoistochemical expression of type V STTR in 2 patients, a mild SSTR5 (score 2) in 5 patients. With regard to SSTR2A, we found a high expression (score 3) in 3 patients and a mild expression (score 2) in 3 patients. In the remaining cases, both SSTR5 and SSTR2A expression was considered negative. Mean duration of Pasireotide Lar treatment was 173.6 months (SD: 650). 24 patients were treated with Pasireotide Lar 60 mg monthly and the remaining 7 patients with Pasireotide Lar 40 mg monthly. Among patients enrolled in CSOM230C2402 study, 14 cases reached the biochemical control of acromegaly. Among patients on post-marketing treatment with Pasireotide Lar, 4 patients were on combination therapy with Pasireotide Lar, Pegvisomant and Dopamine Agonist. At the last examination, 20 patients were on treatment with Pasireotide Lar: 10 patients who had started therapy during CSOM230C2402 clinical trial and all the patients started Pasireotide Lar as compassionate use or post-marketing. All 20 patients documented normalization of GH and IGF-I secretion. In a single case, at neuroradiological follow-up, volumetric reduction of residual pituitary adenoma occurred.
Conclusion
Our data confirmed the efficacy of Pasireotide Lar in aggressive acromegaly.

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P876

The change in metabolic parametres of prolactinoma patients after therapy intervention

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Introduction
Prolactinoma is the prolactin secreting tumor of the pituitary gland which exerts mainly hypogonadal complaints and sometimes symptoms due to mass effect. Meanwhile it was mentioned to cause metabolic abnormalities such as increased fasting plasma glucose (FPG), Low Density Lipoprotein(LDL) cholesterol and triglycerides(TG). We studied whether some of these metabolic parametres of prolactinoma patients could be changed after the therapy.
Methods
This study was in retrospective design, enrolled 100 prolactinoma patients who were admitted to our endocrinology department. 49 of them did not require any treatment. 51 patients who were administered only drug therapy or both surgery and afterwards drug therapy were included. The drugs were cabergoline and bromocriptine. Metabolic variables and tumor dimensions on magnetic resonance imaging (MRI) were studied at diagnosis and after therapy.
Results
Out of 51, 42 were female (82.4%) and nine (17.6%) were male. The age and disease duration did not vary according to sex. 4/9 (44.4%) of male and 7/42 (16.7%) of female harbored macroadenoma. Only three patients underwent pituitary surgery. Through whole group, LDL cholesterol (from 115.3 ± 10.7 to 84.6 ± 14.7, p:0.049) decreased significantly and TG level (from 150.5 ± 26.3 to 121.7 ± 18.5, p:0.30) decreased nonsignificantly accompanying a significant decrease in PRL levels (from 108.6 ± 13.0 to 13.6 ± 2.2, p:0.000) following treatment. The data were shown in detail in Table 1.
Conclusion
Metabolic variables such as FPG, HDL and TG did not show significant alteration while LDL decreased minimal significantly after achievement of PRL level's

normalization in our study. Previously, it was denoted FPG, TG and LDL decreased ($P<0.005$) after prolactinoma treatment, independent of BMI reduction or sex hormonal change. However, the initial metabolic conditions of their patients could be more undesired than our subjects', that might be one reason for much willingness of their values to improve by treatment. Therefore, more studies in prospective design with higher number of patients is required to deliver more accurate results about this scheme.

Table 1 The characteristics of prolactinoma patients before and after the treatment.

	Time of diagnosis	After the treatment	*p* value
PRL (mcg/l)	108.6±13.1	13.6±2.2	0.000
FPG (mg/dl)	94.4±22.6	95.5±16.3	NS
LDL cholesterol (mg/dl)	115.3±10.7	84.6±14.7	0.049
HDL cholesterol (mg/dl)	51.6±4.4	47.9±3.3	NS
TG (mg/dl)	150.5±26.3	121.7±18.5	NS

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P877

"Silent" ACTH-secreting pituitary carcinoma: case report

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Introduction
Pituitary carcinomas are extremely rare neoplasms and molecular events leading to malignant pituitary transformation are largely unknown.
Case report
36-year-old man turned to the clinic for visual and oculomotor disorders. A large endo-supra-latero(S)sellar tumor was found on MRI. There was also an increase in the level of ACTH in the blood (60,80 pmol/l (normal values 5–49)). The level of free cortisol in 24-hour urine was normal. Endoscopic transsphenoidal tumor removal was performed. Histological conclusion was pituitary adenoma (Ki67 10–15%). Immunohistochemical study revealed the expression of ACTH by a tumor. A month after the operation, MRI control was performed. A tumor recurrence was detected. PET-CT revealed metastases in the spine, liver and tubular bones. In the metastasis of the brachial bone, the expression of ACTH was also found. The patient was carried out the combined treatment including 18 courses of palliative chemotherapy (docetaxel, carboplatin, irinotecan, cisplatin, temodal), 3 courses of stereotactic irradiation for primary tumor and therapy with cabergoline and somatostatin analogues. The patient lived 2 years and 9 months after detection of the tumor was made.
Conclusions
There was a decrease in size of the primary tumor after radiotherapy, and chemotherapy resulted in a decrease in the metabolic activity of metastases which increased the life expectancy of the patient.

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P878

Abstract withdrawn.

P879

Radiotherapy for pituitary adenomas – safety and efficacy analysis

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Introduction
Radiotherapy (RT) has been proven to be effective in controlling hormone production and tumor growth in pituitary adenomas (PA). Still, RT adverse effects had turned it an unattractive choice of treatment. The aim of this study was to evaluate the efficacy and safety of RT for patients with PA.
Methods
We conducted a retrospective study of patients treated in our center, a central hospital, since 1998. Thirty-three patients were included, 67% female, with a medium time of follow-up of 85.5 months (P25-44/P75-133 range 11–279). Twenty-nine patients had macroadenoma and 16 cavernous sinus invasion. Eight patients had pituitary deficits before RT. In all but one patient, RT was a secondary treatment after surgery. Eighteen patients had functioning PA (FPA) (11-GH, 6-ACTH, 1-PRL) and 15 non-functioning PA (NFPA) (7 null-cell, 4-FSH, 4-ACTH, 1-PRL).
Results
Twenty-eight patients were submitted to conventional or fractioned stereotaxic RT (mean daily dose 2.26±1.1Gy; mean dose 46.50±9.2Gy) and 5 patients were submitted to radiosurgery (mean dose 23±6.2Gy). Mean age on 1st surgery was 43.31±13.4 years and at RT was 48.94±13.7 years. During follow-up patients presented: visual deficit deterioration ($n=1$,3.1%), new visual deficit ($n=2$,6.2%), hormonal deficit deterioration ($n=3$,37.5%), de novo hormonal deficit ($n=14$,58.3%), stroke ($n=2$,6.2%), cognitive impairment ($n=6$,18.8%) and death ($n=2$). Medium time to development of 1st pituitary deficit was 19 months (P25-9/P75-42). Hypocortisolism and hypothyroidism were the most common deficits ($n=13$). In respect to NFPA, 2 did not achieve tumor growth control and 1 presented tumor growth, requiring new surgery. In respect to FPA: 4 achieved remission, 6 control with pharmacological treatment, 6 did not achieve biochemical control, 1 was lost to follow-up and 1 died. Medium follow-up time to biochemical control was 24 months (P25-11.5 P75-66). Nowadays, 10 patients are under pharmacological treatment. The overall estimated 6-month, 30-months and 108-months pituitary function preservation rates were 87.5%, 57.5% and 30.7%, respectively.
Conclusions
After RT, 86% of NFPA patients presented tumor growth control and 62.5% of FPA presented remission or biochemical control. RT-induced hypopituitarism was the most common adverse effect and hypocortisolism and hypothyroidism were the most common deficits. RT demonstrated to be an effective treatment in PA, nevertheless, it also presented important adverse effects. Life-long follow-up is essential in these patients and a longer follow-up is needed to evaluate long-term outcomes of RT in PA.

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P880

Usefulness of stereotactic radiotherapy in acromegalic patient resistant to conventional treatment

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Introduction
Acromegaly is a rare, chronic disease characterized by increased secretion of growth hormone, most commonly by autonomous adenoma of the anterior pituitary. Mortality is 2–3 times higher than in general population. So that, it is vital to achieve biochemical cure. We present a case in which patient was successfully treated with stereotactic radiotherapy (SRT)- CyberKnife and preserved pituitary function.
Case report
A 39-years old men was admitted to endocrinological outpatient department due to signs and symptoms suggestive for acromegaly. He noticed changes in his face shape, enlargement of hands and feet. He complained about excessive sweating and headache. Laboratory results confirmed diagnosis and excluded hypopituitarism. MRI of pituitary gland revealed microadenoma (8×6 mm), which did not

compress optic chiasm. Before transphenoidal resection of the lesion patient received three octreotide injections. After surgery due to persistent disease, octreotide was re-introduced (dose: 30 mg/monthly). Then, because of drug intolerance, it was replaced with lanreotide (120 mg/monthly). Still, we did not achieve treatment goals. Patient refused to be re-operated. Finally, he underwent stereotactic radiotherapy (CyberKnife). Lanreotide was withdrawn twelve months after SRT. On regular check-up, 18 months after radiotherapy, patient met the criteria of cured acromegaly. Function of other pituitary axes was preserved.

Conclusions

Radiotherapy in acromegalic patients might be useful in case of uncontrolled disease and drug intolerance after surgery. Radiotherapy may lead to biochemical control, thereby limiting the necessity of lifelong medical therapy. SRT is recommended over conventional radiotherapy due to lesser side effects, shorter time to achieving remission and shorter treatment duration.

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P881

Subclinical left ventricular dysfunction in patients with naive acromegaly assessed by two-dimensional speckle tracking echocardiography (2D-STE)

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Introduction

Cardiac disease called acromegalic cardiomyopathy may be present in patients with acromegaly at diagnosis, however most echocardiographic studies showed that systolic function in these patients is normal. Speckle tracking echocardiography (STE) is a novel method that allows for the study of global longitudinal strain (GLS), a marker of early and subclinical left ventricular (LV) systolic dysfunction.

Objective

To evaluate left ventricular GLS in patients with naive acromegaly with normal LV systolic function.

Patients and methods

Fifty-one consecutive patients with naive acromegaly with normal systolic LV function measured by ejection fraction (EF), and a control group were matched for age and gender underwent 2D-STE.

Results

The mean GLS was significantly lower in acromegaly group than in the controls (in%, -17.28 ± 4.9 vs. -20.9 ± 3.2, $P < 0.01$). Majority of acromegalic patients (60.7%) had abnormal GLS. Patients with impairment in GLS had statistically significant longer duration of acromegaly symptoms compared to those with normal GLS values (years, 10.0 vs. 5.0, $P < 0.05$). Acromegalics with lower GLS had also statistically significant increase in parameters of LV thickness i.e. intraventicular septum (IVS) [in mm, 13 (8–19) vs. 11.5 (8–14), $P < 0.05$] and posterior wall (PW) [in mm, 13 (8–17) vs. 12 (9–13) $P < 0.05$] compared to those with normal GLS values. Mean left ventricular mass index (LVMi) was increased in the acromegaly group compared to controls (in g/m^2, 138.8 ± 36.5 vs. 99.4 ± 24.0, $P < 0.01$). There was a statistically significant negative correlation between LVMi and GLS ($R = -0.38$, $P < 0.01$)

Conclusions

Naive acromegalic patients presented with lower GLS compared to the control group. This finding indicates subclinical systolic dysfunction in the untreated acromegalic patients. It cannot be ruled out that the LV function measured with GLS improves as an effect of treatment; it requires further studies. We found longer disease duration in a group of acromegalic patients with impairment in GLS compared to those with normal values. Increased efforts should be made to diagnose acromegaly at early stage to prevent cardiac systolic dysfunction.

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P882

Efficacy and tolerability of cabergoline in a cohort of 160 prolactinomas at weekly doses of up to 9 mg

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Background

Dopamine agonists are the mainstay of treatment for prolactinomas. Cabergoline (CAB) is preferable to bromocriptine due to its greater efficacy and better tolerability.

Subjects and methods

The aim of this retrospective open trial was to evaluate the efficacy and tolerability of CAB in a cohort of 160 patients with prolactinomas routinely followed in Pernambuco Endocrine Research Center and Division of Endocrinology, Hospital das Clinicas, Federal University, Recife, Brazil.

Results

A total of 160 patients (100 women and 60 men; mean age, 31.1 ± 6.3 yrs; age range, 15–44; 86 micros and 74 macroprolactinomas) were enrolled. Overall, 7 patients (4.4%) were intolerant to CAB due to gastrointestinal and/or neurological side-effects (headaches and dizzness). Among the remaining patients, normalization of prolactin (PRL) levels was achieved by 115 patients (75.2%) at doses of up to 2 mg/week, whereas PRL normalization was found in 13 additional patients when CAB dose was increased to up to 3 mg/week. The remaining 25 patients were submitted to increasing doses of CAB up to 9 mg/week, 18 of whom (72%) reached PRL normalization. No patients benefited from weekly doses > 7 mg. Among responsive patients with macroprolactinomas, 82% experienced tumor shrinkage $>50\%$ whereas 55% had complete tumor disappearance. CAB doses > 3 mg/week were well tolerated and no significant valvular abnormalities were found despite the use of weekly doses as high as 9 mg.

Conclusions

In doses of up to 9 mg/week, longterm CAB therapy was well tolerated and enabled PRL normalization in 95% of patients with prolactinomas. No patients benefited from doses > 7 mg/week.

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P883

Pituitary apoplexy: 15 years of experience

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Introduction
Pituitary apoplexy (PA) is an endocrine emergency and usually presents with sudden headache and visual fields changes. Pituitary function assessment should be performed promptly and repeated throughout follow-up, regardless of the choice of treatment.
Methods/design
Retrospective analysis of patients diagnosed with PA admitted to an Endocrinoloy Department of a tertiary hospital between 2002 and 2017. Review of patients' medical records and assessement the following parameters: clinical evaluation, imaging, pituitary deficiencies and treatment at the time of the episode, two months later and by the last evaluation.
Results
We evaluated 17 patients (65% were male), mean age 55 ± 18 years, mean follow-up time 3 years. Four patients had personal history of pituitary adenoma, two of which were non-functioning and two, ACTH-secreting. Hypertension and antiplatelet therapy were the most frequently identified risk factors. Clinical presentation included sudden headache in all patients, decreased visual acuity (38%), visual field deficit (35%) and ophthalmoparesis (43%). A pituitary adenoma was identified in 11 of the 13 patients without known pituitary disease (median diameter: 25 mm). At the time of the apoplexy, hypogonadism was detected in 11/14 patients, hypothyroidism in 9/16, adrenal insufficiency in 5/13 and growth hormone deficiency in 6/13. Twelve patients underwent surgical treatment. Histological analysis revealed gonadotroph adenoma in 4 patients, corticotroph in 2, somatotroph in 2, lactotroph in 1, null cell in 1 and necrotic findings in 2. At the time of hospital discharge, 13 patients were receiving hydrocortisone and 7 levothyroxine. Most of the operated patients had persistence of disease on imaging test after 3–6 months (7/11). At the time of the last evaluation, most patients had insufficiency of two or more pituitary axes. The most common deficits were adrenal (11/16) and gonadal (10/16). There was recovery of ophthalmologic impairment in most operated patients who initially presented with ophtalmoparesis/visual field deficits (6/7).
Conclusion
In this study, surgical treatment was the preferred therapeutic option, which allowed for recovery of visual impairment, despite little recovery of pituitary insufficiency. Patients submitted to conservative treatment had a favourable outcome. Despite being an endocrine emergency, pituitary apoplexy can have a favourable outcome if correctly identified and treated.

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P884

Clinical and treatment outcomes in patients with craniopharyngiomas – single center experience

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Craniopharyngiomas are rare and histologically benign tumors that are associated with an unfavourable prognosis and controversial optimal treatment. The aim of this retrospective study was to review clinical presentation, natural history and therapeutic outcomes of patients with craniopharyngiomas treated in a single center between 1995 and 2017. In that period, 38 patients (16 children and 22 adults) were diagnosed with craniopharyngioma. Median age at the time of diagnosis in children and adults was 12.5 years (range 6–17) and 40 years (range 19–66), respectively. The most frequent presenting feature was visual field defect in adult patients and headache with intracranial hypertension in children (75% and 69%, respectively). In 16 adults and in 10 children hypothalamic invasion was present on initial MRI, whereas optic chiasm impingement was found in 20 adults and 11 children. Fifteen patients underwent gross total resection of the tumor, 13 patients had partial resection of the tumor combined with radiotherapy (RT), 4 patients had two partial resections together with RT, while 6 patients had partial resection of the tumor and are awaiting further treatment. During a follow-up period of 56.5 months (range 3–264) 10 out of 15 patients had tumor relapse after gross total resection, while 7 out of 17 patients had progression of residual tumor after the partial resection(s) combined with RT. There was no difference in recurrence/progression rate with regard to therapeutic approach (gross total resection vs. partial resection with RT). Median time to recurrence/progression was 36 months (range 8–156). There was no difference in time to recurrence/progression between patients who underwent gross total resection and those with residual tumor. Hypopituitarism and diabetes insipidus (DI) were found significantly more often after the treatment in all patients ($P < 0.001$), while body mass index (BMI) significantly increased one year after the treatment (22.4 kg/m^2 (15.3–26.1) vs 28.1 kg/m^2; $P < 0.001$). There were no statistically significant differences in the incidence of hypopituitarism, DI and obesity regarding therapeutic approach. Our results showed no differences in progression-free survival and the incidence of hypopituitarism, DI and obesity between gross total resection and partial resection with RT.

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P885

Very high prolactin levels associated to domperidone therapy

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Introduction
Prolactin (PRL) levels $>$ 250 ng/ml are highly suggestive of prolactinomas though they may be also seen in other conditions, particularly macroprolactinemia, GH and PRL cosecreting tumors, and renal failure. Drug-induced hyperprolactinemia is typically associated with mild PRL elevation (usually $<$100 ng/ml). Higher levels (around 300 ng/ml) have been occasionally reported, particularly with risperidone, an atypical antipsychotic drug.
Case report
A 25 year old asymptomatic women was referred to the endocrinologist with the diagnosis of a microprolactinoma. In a routine lab evaluation, PRL levels of 720 ng/ml (15120 mIU/l) e 690 ng/ml (14490 mIU/l) were found (normal range, 2.8–29.2 ng/ml [59–613 mIU/l]). A 0.5 cm pituitary lesion was subsequently shown on a MRI scan. Macroprolactin screening was negative. Thyroid and renal functions were normal. The physical examination do not identify noteworthy findings. The patient has been treated with a combined oral contraceptive pill for 24 months and with domperidone (a prokinetic drug) over the past 3 months (in the treatment of functional dyspepsia). Two months after domperidone withdrawal, PRL levels dropped to 18 ng/ml (328 mIU/l).
Conclusion
This case shows that domperidone should be included in the list of drugs that may be associated with very high PRL levels. The lesion depicted on MRI scan was a nonfunctional pituitary microadenoma.

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P886

Acromegaly: surgical results and predictors for remission

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Introduction
Acromegaly is a rare disease with significant morbidity and mortality. Surgical treatment is the first line treatment for these patients, with remission rates of $>$85% for microadenomas and 40–50% for macroadenomas.

Objectives
Our objective was to characterize patients with acromegaly followed in our department and evaluate remission status after surgery. We also aimed to determine remission related factors.
Methods
A retrospective study was performed. Patients diagnosed with acromegaly in the last 12 years and submitted to surgery were included. The following data was collected: age at diagnosis, gender, follow-up period, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) values before and 3–6 months after surgery, adenoma size and invasion of the cavernous sinus, therapeutic strategies and response to therapy.
Results
We included 41 patients. 53.7% ($n=22$) were female. Mean age at diagnosis was 47.8 years (S.D. = 11.9). Mean follow-up was 6 years (S.D. = 3.3). Diagnosis was based on phenotypic alterations in the majority of patients (51.2%, $n=21$). At diagnosis GH value ranged from 0.4 to 80.2 ng/ml (median 11.9) and IGF-1 value ranged from 288 to 1610 ng/ml (median 646). The majority of patients had a macroadenoma (78%, $n=32$); 36,6% ($n=15$) had invasion of the cavernous sinus. After surgery, median levels of GH and IGF-1 were 1.9 (min. 0.05, max 37.4) and 333.5 (min. 33.5, max. 1130) respectively. 12.2% ($n=5$) were submitted to a second surgery and 7.3% ($n=3$) to radiotherapy. 56.1% ($n=23$) of the patients were treated with medical therapy after the surgery. During follow-up 1 patient was lost and two patients died. Of the remaining patients 44.7% ($n=17$) had remission criteria, 31.6% ($n=12$) had controlled disease under medication and 23.7% ($n=9$) had active disease. Remission status was significantly correlated with GH value before and after surgery ($P=0.016$ and $P=0.004$ respectively) and IGF-1 value after surgery ($P<0.001$). Invasion of the cavernous sinus was also associated with lower remission frequency ($P=0.004$).
Conclusion
Remission status after surgery for acromegaly was similar to that described in the literature. The main features correlated with remission were GH value before and after surgery, IGF-1 value after surgery and invasion of the cavernous sinus.
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P887

Investigation and initial management of hyponatraemia
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Hyponatraemia is the commonest electrolyte disturbance in clinical practice and accounts for 15–20% of emergency admissions to hospital. It is thought that up to 30% of hospitalized patients develop a degree of hyponatraemia at some point during their admission. It is therefore an important problem. Management of inpatients with hyponatraemia remains problematic and an audit of our practice at St Mary's Hospital, Imperial College Healthcare NHS Trust, has confirmed that. The audit was conducted on the management of severe hyponatraemia (defined as serum sodium level 125 mmol/l) in medical and surgical adult inpatients over a 3-month period, between October 2012 and December 2012. The audit findings indicated the need for further education and training with regards to the management of hyponatraemia within the general medical and surgical specialties, as well as the need for the introduction of a guidance which includes helpful steps in the accurate assessment and initial treatment of patients with hyponatraemia. Our Endocrine team created a protocol that describes the early identification of hyponatraemia and management strategies, especially when it is severe. The guidance indicates that all patients with severe hyponatraemia should have their volume status established and documented clearly, appropriate biochemical assessment in the form of paired plasma and urine osmolalities and urinary sodium measurements and endocrine specialist input in some form, as inpatients, as well as a definitive diagnosis for the hyponatraemia prior to discharge. The guidance relates to all junior and senior medical staff that cares for adult inpatients. Dedicated training was provided to medical staff to familiarize themselves with the protocol. Following its implementation, we decided to audit the adherence to this guidance. The study included all adult medical and surgical inpatients at St. Mary's Hospital with sodium level equal to or less than 125 mmol/l during the period 1–31 March 2016. The results demonstrated that the patients' volume status was clearly established in 51% cases, osmolalities and urinary sodium were measured in 21% cases, endocrine review was performed in 13% cases and definitive diagnosis for the hyponatraemia was made in 60% cases. In the majority of cases the hyponatraemia was treated successfully. It is possible that following the implementation of the Hyponatraemia Guideline the non-endocrine teams feel more confident in managing the above electrolyte abnormality without seeking specialist advice. We plan to continue the training of our staff and re-audit in spring 2019.
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P888

Lanreotide autogel may be an effective approach for acromegalic patients who failed octreotide lar
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Background
Growth hormone secreting pituitary gland adenomas specifically express somatostatin (SST)-2 and SST5 receptors. First-generation somatostatin analogs (octreotide and lanreotide) are the mainstay in the medical treatment of acromegaly, however the percentage of patients controlled with these drugs significantly varies in the different studies (20–70%). Many factors are involved in the resistance to SRL somatostatin analogs such as sst, AIP, E-cadherin, ZAC1, filamin A and β-arrestin expression in the somatotropinomas. With a higher affinity for the SST2 receptors and low affinity for the SST-5 ones, octreotide and lanreotide are thought to have a similar efficacy in normalizing IGF-1 and GH levels. However, their exact dose equivalence is not yet fully established.
Objective
To evaluate the effectiveness of Lanreotide autogel (LAN) 120 mg monthly in normalizing GH and IGF-1 levels in acromegalic patients who failed octreotide LAR (OCT-LAR) 30 mg monthly concerning hormonal normalization. These doses have usually been considered the maximal doses of these agents.
Subjects and methods
Twenty four patients (14 men and 10 women; mean age 42.3 ± 10.2 years [range, 25–62 years]) who do not reach normalization of IGF-1 levels while taking OCT-LAR 30 mg every 4 weeks intramuscularly were enrolled. These patients have been previously treated with OCT-LAR only ($n=15$) or OCT-LAR combined with cabergoline ($n=9$). They were given subcutaneous injections of LAN 120 mg every 4 weeks instead of OCT-LAR. The clinical and biochemical responses of patients were evaluated 3 months later.
Results
After 3 months of LAN treatment, normalization of IGF-1 levels and GH levels < 1 ng/ml were observed in 6 patients (25%). The response rate did not differ in patients previously submitted to OCT-LAR monotherapy or those receiving combined therapy. The LAN tolerability profile was similar to that of OCT-LAR.
Conclusion
Our results indicate that monthly injections of 120 mg of Lanreotide autogel may be an effectivel approach for one quarter of acromegalic patients partially responsive to 30 mg of OCT-LAR monthly.
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Poster Presentations: Reproductive Endocrinology

Adrenal Cortex (to include Cushing's)

P889

Are there specific biomarkers able to differentiate non classical congenital adrenal hyperplasia (NCAH) due to 21-hydroxylase deficiency from non-NCAH in a population of naive hyperandrogenic women in the reproductive age?

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Objective

This study was aimed to evaluate the prevalence of non classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-NCAH) in hyperandrogenic women in the reproductive age attending our Endocrinology Unit and to identify specific phenotypic traits among clinical, biochemical and hormonal features.

Setting

Outpatient Unit of Endocrinology, S. Orsola-Malpighi University Hospital of Bologna, Italy.

Patients and methods

Among a population of 1079 women who attended our Unit from 2003 to 2017 for hyperandrogenic complaints, we selected 70 subjects having basal 17 hydroxyprogesterone (17OHP) levels in the follicular phase of the menstrual cycle $\geq$200 ng/dl measured by immunoassay. All these 70 patients performed CYP21A2 gene analysis by direct DNA sequencing and multiplex ligation-dependent probe amplification (MLPA). They also performed an ovarian ultrasonography, a 1-24ACTH test, a complete basal steroid profiling measured both by immunoassay and by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), all in the follicular phase of the menstrual cycle.

Results

Twenty-three patients resulted affected by 21-NCAH, 15 were found to be heterozygotes for the 21-hydroxylase deficiency (21-HTZ) and 32 had no mutations for CYP21A2gene(C). As expected, these three groups resulted significantly different for basal 17OHP levels measured by immunoassay even though there was an overlap among them [21-NCAH:1971$\pm$2550 ng/dl (from 228 to 12,420); 21 HTZ: 287$\pm$85 ng/dl (from 196 to 452); C: 305$\pm$100 ng/dl (from 201 to 624)]. At variance, basal 17OHP measured by LC-MS/MS discriminated the 21-NCAH group from the others without any overlap [21-NCAH: 16.9$\pm$23.1 ng/ml (from 3.5 to 51.5); 21 HTZ: 1.7$\pm$0.9 ng/ml (from1.1 to 2.9); C: 1.4$\pm$0.3 ng/ml (from 1.1 to 1.8)]. Furthermore, in 21-NCAH patients 21-deoxycortisol levels were found significantly higher than in the other groups (0.58$\pm$0.32 ng/ml vs. 0.14$\pm$0.08 ng/ml in 21 HTZ and 0.11$\pm$0.06 ng/ml in C, $P<0.05$). In addition, cortisol and corticosterone measured by LC-MS/MS were significantly lower in 21-NCAH group (cortisol: 61.6$\pm$46.9 ng/ml; corticosterone 1.1$\pm$0.9 ng/ml) than in 21-HTZ (cortisol: 182$\pm$27 ng/ml; corticosterone: 12.1$\pm$9.7 ng/ml) and C (cortisol: 169$\pm$26 ng/ml; corticosterone 14.4$\pm$5.2 ng/ml) groups.

Conclusion

This study confirms that the prevalence of 21-NCAH of new diagnosis among hyperandrogenic women in the reproductive age is high accounting for 2.2%. In addition, it demonstrates that a basal blood steroid profiling measured by LC-MS/MS in the follicular phase of the menstrual cycle and composed by 17OHP, 21-deoxycortisol, cortisol and corticosterone is a valid diagnostic tool in 21-NCAH patients.

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Bone & Osteoporosis

P890

Bone mineral density in oligomenorrhoeic women with polycystic ovary syndrome

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Introduction

Oligomenorrhoea have negative impact on bone mineral density (BMD). The aim of this study was to analyze BMD in oligomenorrhoeic women with polycystic ovary syndrome (PCOS), and healthy controls with regular menstrual cycles.

Methods

We analyzed 29 women with PCOS diagnosed using ESHRE/ASRM criteria (age: 23.6$\pm$4.7 years, BMI: 24.9$\pm$6.1 kg/m^2) and 22 healthy BMI-matched controls (HC) (age 31.6$\pm$6.3 years, BMI 24.9$\pm$6.1 kg/m^2). In follicular phase of menstrual cycle we determined BMD by osteodensitometry, fasting serum glucose (FG), insulin, lipids, calcium, phosphate, albumin, PTH, testosterone, SHBG, DHEAS, 17OH-progesterone, androstenedione, estradiol, TSH, fT4, fT3. HOMA, FAI and corrected calcium were calculated. Differences between groups were age-adjusted.

Results

There was no difference between groups in BMD measurements on L1-L4, total and neck femur. PCOS had higher testosterone (2.4$\pm$0.8 vs. 1.4$\pm$0.5 nmol/l, $P=0.002$), androstenedione (3.2$\pm$1.1 vs. 1.9$\pm$0.4 ng/ml), corrected calcium (2.2$\pm$0.9 vs. 2.1$\pm$0.9 mmol, $P=0.011$). There were no between-groups differences in other measurements. PCOS women showed significant correlation between L1-L4 BMD and LH ($r=0.49$, $P=0.04$), L1-L4 BMD and DHEAS ($r=-0.68$, $P=0.001$), total femur BMD and TSH ($r=-0.56$, $P=0.012$), and total femur BMD and PTH ($r=-0.65$, $P=0.022$).

Conclusions

Oligomenorrhoeic women with PCOS did not differ in BMD to the BMI matched healthy controls.

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Cardiovascular Endocrinology and Lipid Metabolism

P891

Effect of mifepristone on viability of cells of HECa10 line evaluated in real time depends on the duration of exposure and density of cells and allows choosing the proper time point to apoptosis assessment

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Apoptosis is an important process influencing tissues growth, however the assessment of this process in monolayer culture is difficult because apoptotic cells disappear quickly due to secondary necrosis. Most of the methods used with success in vivo is useless in vitro. Our approach to evaluating apoptosis *in vitro* is based on the possibility to perform multiple assays on the same sample well. The aim of the study was to evaluate the effect of mifepristone (RU-486), a strong competitive antagonist of progesterone and glucocorticoid receptors, used at the previously selected concentration of 2×10^{-5}M on viability of cells of the HECa10 high endothelial line assessed in real time and on apoptotic intensity assessed in cultures carried out with different numbers of sown cells: 1000, 2000, 4000 and 8000 cells/well in a 96-well plate. Two compatible assays were used: luminescence method for assessment of cell viability in real time and fluorescence method for apoptosis detection based on activities of caspase-3 and 7 (Promega Corporation). It was shown that the longer the exposure time to mifepristone and the higher the cell density in the wells, the inhibitory effect of mifepristone on viability of cells is earlier and stronger (observed already after 2 hours for 8000 cells/well, after 4 hours for 4000 cells, and only after 24 hours for 1000 and 2000 cells/well). The inhibitory effect of mifepristone grew with the duration of the culture what allowed to choose the right time point for the assessment of the apoptosis intensity. After 26 hours mifepristone caused an increase in apoptosis e.g. by 19% for 8000 cells and by 15% for 1000 cells/well. At that time point mifepristone inhibited cell viability e.g. by 40% for 8000 cells and by 20% for 1000 cells/well. Tracing the viability of cells in controls found out that the luminescence signal remains linear for 1000 and 2000 cells/well over the 3 day period, whereas the signal from higher cell number (4000 and 8000 cells/well) lose linearity after 48 hours. Mifepristone, a drug commonly used as medical abortion, evokes strong antiangiogenic effect on HECa10 line via inhibition of cells viability and induction of apoptosis.Tracing the viability of cells in cultures in real time allows to choose the optimal time to complete the culture and to determine the apoptosis intensity under the influence of mifepristone.

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P892

An analysis of the cardiovasular risk factor profiles of patients with turner syndrome

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Turner Syndrome (TS) is a genetic disorder which affects 0.5–1 in every 2000 females. It is a multi-systemic disease characterised by a deleted or partially missing X chromosome. This deletion results in a higher incidence of primary ovarian failure and removal of the cardio-protective presence of endogenous oestrogen. The aim of this study was to analyse the prevalence of cardiovascular risk factors in a TS cohort and to assess the steps taken to modify these risk factors. We retrospectively analysed the charts of 54 TS patients attending a university hospital endocrinology clinic. Data was collected on blood pressure (BP), lipid and Haemoglobin A1c profiles, statin and hormone replacement therapy (HRT) use, Body Mass Index (BMI), and the presence of structural heart disease. Data is expressed as mean $\pm$S.D. We aimed to assess the number of patients who reached targets of blood pressure (BP) less than 140/90 mmHg; BMI <25 kg/m^2 and Low density lipoprotein (LDL) less than 2.6 mmol/l. Fifty four patients with mean age of 35.1 ± 12.6 years had BMI of 28.54 ± 8.11 kg/m^2; 19 patients had a BMI within target. Mean BP was $121.6 \pm 13.3/73.7 \pm 10.5$ mmHg. Twelve patients were on anti-hypertensive agents (eight patients were on single agent treatment and four were taking two agents). Mean BP of those not on anti-hypertensive therapy was $117.3 \pm 12.2/72.2 \pm 10.5$ mmHg. Seven patients did not have blood pressure within target. Mean LDL level was 2.95 ± 1.31 mmol/l with mean total cholesterol of 5.11 ± 2.62 mmol/l. Only 12 out of 54 (22%) of patients achieved their LDL targets. Seven patients were on therapy while a further four declined therapy. Mean LDL of those on therapy (6 on statin therapies; one on ezetimibe) was 3.4 ± 0.6 mmol/l. One patient on statin therapy achieved the target LDL. Mean HbA1c for the cohort was 34 ± 3.6 mmol/mol. Four patients had impaired glucose tolerance (IGT). Three patients had confirmed type 2 Diabetes Mellitus (T2DM) with mean HbA1c of 54.0 ± 9.9 mmol/mol. Fourteen patients were not taking hormone replacement therapy; six patients were post-menopausal, three patients desired pregnancy, three patients had spontaneous menstruation, one patient declined therapy and one patient had severe liver disease. In summary, while the majority of patients in our cohort have a blood pressure within our recommended targets a significant number are above both their BMI and LDL targets. Further efforts will be concentrated on improving these metabolic goals.

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Clinical Case Reports - Thyroid/Others

P893

A testicular mass in a patient with Klinefelter syndrome

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A 35 year old gentleman with a history of 47 XXY Klinefelter Syndrome (KS) and previous orchidopexy presented to the endocrine service with a two-week history of left sided testicular pain. Examination revealed a tender left testicle. Testicular ultra-sound confirmed bilateral atrophic testes and a 5 mm hypoechoic lesion in the left upper pole. This patient presented with KS at the age of 15 years with gynaecomastia and elevated gonadotrophins. After urgent urological review a left radical inguinal orchidectomy was performed. Histology revealed a sex cord-stromal tumour, 20 mm in maximum measurement. The major pattern was multifocal Leydig cell tumour with additional glandular ductal components. There was no normal testicular histology and no evidence of malignancy. The patient remains clinically well six months post-operatively.

Discussion

KS is the most common sex chromosomal disorder in males, caused by the inheritance of at least one additional $\times$ chromosomes from either parent. Its prevalence is 1 in 660. Discovered in 1942 by Harry Klinefelter, it is characterised by gynaecomastia, aspermatogenesis and elevated gonadotrophins. Sex cord stromal tumours (SCST) are rare, accounting for only 5% of all testicular tumours in general populations. These tumours occur most commonly between 40 and 50 years of age and rarely metastasise. Patients who develop metastasis have an estimated prognosis of two years. Leydig cell tumours are the most common type of SCST. Approximately 30% present with virilising or feminising symptoms due to excess androgens or oestrogens. Two large epidemiological studies (Swederlow *et al*. 2005 and the Danish Cytogenic Registry), have demonstrated that KS is not associated with an increased risk of testicular tumours. Despite a 37% prevalence of crypto-orchidism, few testicular cancer cases are seen. These same studies confirmed the greatly elevated risk of lymphoma and breast cancer iin KS patients. Mediastinal germ cell tumours are also observed in KS patients despite being extremely rare in the general population. Two theories exist to explain the discrepancy between the perceived and the actual risk of testicular cancer in this group. One possible explanation is an unknown immunological process which has a net protective effect against testicular cancer. The second hypothesis postulates that patients with undiagnosed KS present with testicular cancer, however the diagnosis of KS is missed due to phenotypical variability and under-recognition. This case highlights the phenotypic variability and complexity of KS. In summary, greater awareness of KS, its potential complications and various manifestations, is needed to optimise patient outcomes.

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P894

Postmenopausal virilization with negative imaging

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Introduction

After menopause, an abrupt drop in estrogen levels happens, while ovary androgens secretion declines gradually with aging. This relative hyperandrogenism may lead to the development of hyperandrogenic symptoms. However, the development of marked hirsutism and/or symptoms/signs of virilization, make necessary a detailed study in order to rule out tumorous cause (from adrenal glands or ovaries).

Case report

58 years old woman with progressive appearance of abundant terminal hairs in face, decrease in scalp hair and deepening of the voice during the last 5 years, worse in the last year. Medical history: smoker, no treatments. Menarche at age 13, regular periods. 4 pregnancies, 1 abortion. Hysterectomy at age 43 due to uterine fibroids. Physical examination: BMI 24.9 kg/m^2, blood pressure 140/80 mmHg; severe hirsutism (Ferriman-Gallwey scale: 32), male type balding, clitoromegaly and centripetal fat distribution without other signs of hypercortisolism. Laboratory evaluation: hematocrit 48.5%, TSH 2.7 μUI/ml (0.35–3.7), FSH 64 μUI/ml (>30), LH 22 μUI/ml (>14), prolactin 5.5 ng/ml (<25), estradiol 26 pg/ml (0–32.2), progesterone 0.7 ng/ml (<1), 17-hydroxy-progesterone 0.89 ng/ml (0.23–1.36), DHEA-S 57.9 μg/dl (80–560), androstenedione 0.83 ng/ml (0.6–3.5), testosterone 6.54 ng/ml (0.14–0.76), serum cortisol levels (after 1 mg overnight dexamethasone) 1.07 μg/dl (<1.8). With these findings, we suspected tumorous cause. However, abdominal MRI, adrenal CT scan, and gynecologic ultrasonography did not show any tumor. After excluding adrenal gland mass, due to the high levels of testosterone, the most reasonable diagnosis was an ovarian tumor eluding detection with imaging so, given the difficulty of performing an ovarian and adrenal venous sampling, Decapeptyl (a GnRH analogue) was prescribed to the patient. GnRH analogues have been shown to normalize testosterone levels in patients with ovarian hyperandrogenism. After Decapeptyl therapy, testosterone levels become normal (testosterone 0.14 ng/ml, FSH 9.33 μUI/ml, LH <0.07 μUI/ml) and we observe an evident clinical improvement, supporting ovarian origin. Therefore, oophorectomy was performed. Histopathology: 4 mm primitive rests in the hilus of right ovary, expecting determination of androgen receptor. Current laboratory evaluation: testosterone 0.16 ng/m, FSH 57 μUI/ml, LH 41 μUI/ml.

Conclusion

Despite it is usual to find hyperandrogenic symptoms after menopause, the development of severe hyperandrogenism or virilization should makes us rule out an organic cause, including tumoral origin. If imaging is inconclusive, GnRH

analogues would be an effective treatment for ovarian virilization in postmenopausal women.

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P895

Hypergonadotropic hypogonadism secondary to vanishing testes syndrome newly diagnosed in a 42-year-old male patient

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Introduction
Cryptorchidism is the most common abnormality of male sexual development. Approximately 5% of cases of cryptorchidism are associated with vanishing testes syndrome. This rare condition occurs when an initially normal testicle that existed in fetal life subsequently atrophies. Affected patients usually have normal male external genitalia and hypergonadotropic hypogonadism. This disease is usually diagnosed in early childhood allowing for normal sexual development with timely testosterone therapy. Here we report the highly unusual case of a 42-year-old male patient with an early onset hypergonadotropic hypogonadism left undiagnosed and untreated for 4 decades, most probably secondary to vanishing testes syndrome.
Case report
Forty-two-year-old african male referred to Endocrinology outpatient clinic due to suspected hypogonadism. Phenotypical features included gynoid body fat distribution, gynecomastia, absent facial and truncal hair, micropenis and no palpable testicles in the scrotum. He denied ever experiencing development of male secondary sex characteristics. His medical/surgical history was unremarkable, to the best of his knowledge. Family history was unknown to the patient. Endocrine testing revealed low testosterone (total testosterone of 46 ng/dl and free testosterone of 1.04 ng/dl), elevated gonadotrophins (FSH 27.7 U/l and LH 15.7 U/L), AMH <0.01 µg/l and a normal thyroid and adrenal axis function results. Peripheral blood karyotype was 46, XY. Scrotal ultrasound confirmed cryptorchidism. Pelvic and abdominal echography and MRI did not suggest any ectopic gonadal structures. Skeletal X-Ray and DXA showed no signs of fractures or osteoporosis. The patient was started on monthly testosterone injections with great clinical benefit, namely: increased energy; improved muscular mass; increased penile length; lower voice pitch and development of axillary, facial and pubic hair with male distribution.
Conclusion
This male patient's clinical course, with failure of normal pubertal progression, along with his endocrinological and radiological presentation suggest a case of late diagnosed early childhood onset hypogonadism. The most likely diagnosis is vanishing testes syndrome, although surgical exploration is yet to be performed. The timing of his diagnosis – during the fourth decade of life – makes this case quite unique. Clinicians should be aware of this condition in face of a male hypogonadic patient, even when presenting during adulthood, if the disease course is suggestive of an early life onset.

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P896

Gender identity and assignment in a 46XY DSD-case report

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Introduction
The term disorder of sexual development (DSD) refers to a congenital condition characterised by a discordance in the development of chromosomal, gonadal and anatomical sex. The inborn errors of metabolism in these disorders due to genetic mutations lead to anomalous genitalia.
Case report
A 16-year-old girl without significant family history was referred to our department for primary amenorrhea. The physical examination revealed: height of 167.5 cm, weight of 68 kg (BMI = 23.8 kg/m^2), Tanner stage 3 for breast development and 5 for pubic hair growth. Inspection of external genitalia showed normal appearance of labia majora with labia minora attached on the ventral side of the clitoris and no visible urethral opening. In addition, the patient had clitoromegaly-microphallus-like appearance and hirsutism. No inguinal masses were palpable. The laboratory findings showed basal plasma cortisol: 19 µg/dl, ACTH: 49.96 pg/ml, androstenedione: 2.65 ng/ml, DHEA-S: 191.9 µg/dl, 17-OH Progesterone: 2.38 ng/ml, FSH: 91.45 mIU/ml, LH: 15.18 mIU/ml, estradiol: 13.6 pg/ml, testosterone: 234.5 ng/dl, dihydrotestosterone: 120 pg/ml, inhibin B: <10 pg/ml, anti-Müellerian hormone: 0.24 ng/ml. The karyotype was performed, revealing a 46 XY male karyotype. An echogenic mass of 28/13 mm on the right inguinal side and the absence of uterus, ovaries and fallopian tubes was identified on abdominal ultrasound. The MRI scan confirmed two masses resembling testes located in both inguinal canals and associating yolk sack, outline of cavernous bodies with no external opening in the pelvic region and on the posterior side of the bladder a seminal vesicle-like mass. After careful expert evaluation performed by a multidisciplinary team, gender assignment decision as female was made, taking into account the patient's wish. In this context, we recommended gonadectomy due to the malignant potential of the abdominal testis-like masses. After surgery, she will receive hormone replacement therapy with estrogens to maintain secondary sexual characteristics.
Conclusions
A comprehensive multidisciplinary team is essential in order to provide the best of care for patient with DSD. Prioritizing patients wish coupled with the specialists' consensus regarding management is probably the best way to treat this medical entity.

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P897

Type 1 autoimmune polyglandular syndrome – clinical case report

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Introduction
Type 1 autoimmune polyglandular syndrome is a rare entity, presenting typically during childhood and comprising a variable combination of autoimmune endocrine and non-endocrine diseases that differ in their immunological features. This phenotypical heterogeneity may difficult the identification of this syndrome.
Clinical case
33 year-old female, presenting with secondary amenorrhoea at the age of 13, and by that date diagnosed with hypergonadotropic hypogonadism (HH) and primary autoimmune hypothyroidism. By the age of 14 she was diagnosed with primary hypoparathyroidism. She has a family history of two maternal cousins presenting with primary hypothyroidism. The height and weight developments were normal. When she was 30 years old she was referred to the adult Endocrinology consultation for follow-up. The patient complained of progressive asthenia during more than one year. Physical examination did not show any relevant findings, namely skin and mucosal hyperpigmentation. The analytical results revealed serum cortisol – 3.7 µg/dl (3.7–19.4), ACTH – 451.7 pg/ml (7.2–63.3), TSH – 3.04 µUI/ml (0.35–4.94), free T4 – 1.42 ng/dl (0.7–1.48), free T3 – 2.34 pg/ml, (1.71–3.71), anti-thyroglobulin antibodies – 6.3 UI/ml (<4.11), anti-TPO antibodies – 14.7 UI/ml (<5.61), ionized calcium – 1.07 nmol/l (1.15–1.35), parathormone – 7.8 pg/ml (15.0–68.3), anti-parietal cell antibodies – positive, vitamine B12 – 328 pg/ml (189–883), creatinine – 1.1 mg/dl (0.6–1.1), urea – 41 mg/dl (15–40) and GFR – 66.20 ml/min/1.73 m^2. OC was temporarily suspended confirming the diagnosis of HH: LH – 39.23 mUI/ml (2.39–74.24),

FSH – 92.22 mUI/ml (3.35–20.82), oestradiol – 19 pg/ml (21–649). The renal echography did not reveal any abnormalities and the bone densitometry showed secondary spinal osteopenia. She is presently medicated with hydrocortisone 15 mg and fludrocortisone 0.05 mg daily due to the primary adrenal insufficiency. She maintains desogestrel 75 µg, L-thyroxine 112 µg, calcium carbonate and initiated calcitriol 25 µg every 12 h.
Conclusions:
Type 1 polyglandular autoimmune syndrome shows not only heterogeneity in respect to the nature of the several possible disease components, but also in regard to their temporal presentation, which in the past was admitted to be more predictable. The positivity to anti-parietal cell antibodies and the decline in the renal function underline the importance of monitoring for the development of pernicious anaemia and tubulointerstitial nephritis.

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P898

Triple X and premature ovarian insufficiency – case report

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Introduction
Triple X syndrome is the most common female chromosomal abnormality, with an estimated incidence of 1/1000 female newborns. Most of the women are phenotypically normal, apart from being taller than average. Possible additional problems are psychiatric disorders, genitourinary malformations, EEG abnormalities, scoliosis and premature ovarian insufficiency.
Case report
46-year-old female, referred to the Endocrinology department due to secondary amenorrhea since 30 years old. Obstetric history of one gestation/one liveborn at 21 years old. Personal history of androgenic alopecia without known aetiology. Irrelevant family history. Medicated with hormonal replacement therapy since last year. Unremarkable physical examination. Height 149 cm, Weight 60 kg. The biochemical study showed an elevated basal Follicle-Stimulating Hormone (FSH) level 43.59 mUI/mL (reference range 2.5–10.2) and Luteinizing Hormone (LH) 23.14 mUI/mL (1.9–12.5) with low estradiol 65.79 pmol/l (71.6–529.2). Further biochemical study was normal, namely sex hormone binding globulin, thyroid function and negative auto-immunity. A transvaginal pelvic ultrasound scan showed no alterations. No osteoporosis or osteopenia verified by DEXA. The karyotype revealed a mosaicism of 47, XXX/46, XX.
Discussion
Genetic defects are proposed to cause premature ovarian insufficiency by increasing atresia of ovarian follicules due to apoptosis or failure of follicle maturation and the decreasing the pool of primordial follicles. We aim to emphasize the need for chromosomal analysis in women with premature ovarian insufficiency leading to primary or secondary amenorrhoea.

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Developmental Endocrinology

P899

A 25 years old male patient with Noonan syndrome and delayed puberty

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Introduction
Noonan syndrome is a genetic disorder that usually occurs on a sporadic basis (de novo mutuations) or with autosomal dominant inheritance. Patients present with dysmorphic facial features, cardiac disorders and short stature. Delay of puberty can also be noted. We present here an adult case of Noonan syndrome.
Presentation
A 25 years old male presented to our department with low stature, decreased libido and absence of any secondary sexual characteristic. Fifteen years ago, he was diagnosed with Noonan syndrome, but had no further management, because he was lost in follow up. On clinical examination his height was 156 cm and his weight 44 kg (BMI:18 kg/m^2). He had the distinctive facial features of the syndrome (triangle-shaped head, wide forehead, hypertelorism, and low-set posteriorly rotated ears), bilateral cryptorchidism, hypoplastic scrotumn, pennis length 5.5 cm, pubic hair Tanner stage II, and absence of facial hair. Laboratory evaluation revealed: testo:0.025 ng/ml, LH: 8.55 mIU/ml, FSH: 40.31 mIU/ml and normal IGF1 for his age (439 ng/ml). His bone age was delayed (12–13 years old), and had osteoporosis of the lumbar spine (T score: −3.1). Testosterone replacement therapy was initiated in order to promote the development of secondary sexual characteristics and the improvement of his muscle mass, bone density and libido.
Conclusions
In patients with Noonan syndrome delayed puberty should be treated in females after the age of 13 with estradiol or conjugated estrogens, and in males after the age of 14 with testosterone, as early as possible. Treatment with GH is also indicated, especially in patients with certain genetic mutations, starting at the prepubertal period to help patients to achieve an adult height and to promote bone growth.

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P900

Abstract withdrawn.

P901

Evaluation of pubertal development in young with type 1 diabetes mellitus: about 200 patients

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Introduction
Puberty is associated with various hormonal changes which can influence glycemic control in youth with type 1 diabetes mellitus, especially with the increase in growth hormone. Conversely, a poor control of diabetes can lead to delayed puberty.
Objective
To assess pubertal status in young patients with diabetes Type 1 and determineÂ factors that influence pubertal development.

Patients and methods
Analytical retrospective study of 7 years in the period ranging between January 2010 and November 2017, in young with type 1 diabetes aged between 14 and 20 years, collected in Endocrinology-Diabetology departement of the University Hospital of Casablanca. Puberty was compared at the stage expected for chronological age. Weight and size were measured and compared with targets (WHO curves). The listed according puberty Tanner was compared stadium expected for chronological age of puberty according to Tanner listed was compared stadium expected for chronological age of puberty according to Tanner listed was compared to the expected stage for chronological age Statistical analysis performed by the software SPSS.16
Results
During the studied period, 200 patients were studied (57% girls, 43% boys), average age of diabetes discovery was 10 ± 2 years. The mean HbA1c level was 11%. A low socioeconomic level was found in 62% of patients. A pediatric transition was noted in 15% of patients. An intensive insulin regimen was adopted in 115 patients (57%). Delayed puberty was found in 11 boys (13%) and in 4 girls (5.3%). Menarche average age was 12 (9–16) years. Irregular menstruations were found in 21% of girls with secondary amenorrhea reported in a girl. Short stature was found in 9 boys and 16 girls. Underweight was seen in 20% of patients, normal weight in 75% and overweight in 5% of cases. Delayed puberty was correlated to glycemic control ($P < 0.05$), with diabetes duration ($P < 0.02$), rural origin ($P < 0.05$) and to repeated hypoglycemic episodes ($P < 0.02$). No significant association regarding the insulin regimen and micro-angiopathy presence ($P < 0.2$) was found.
Discussion
Metabolic control of diabetes and age at diagnosis are major factors influencing growth and pubertal development in young diabetics. It is therefore essential to ensure close monitoring of young diabetics growth and pubertal development and good glycemic control must be maintained.

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Diabetes (to include epidemiology, pathophysiology)

P902

Comparison of diabetes mellitus screening methods for women with polycystic ovary syndrome

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Objective
To compare screening strategies for type 2 diabetes mellitus (DM) and impaired glucose tolerance (pre-DM) in woman with polycystic ovary syndrome (PCOS).
Design
Prospective study.
Patient(s)
Adult women with PCOS ($n = 62$) according to NIH criteria.
Main outcome measure (s)
Subjects were screened for pre-DM and DM using a 2-hour glucose tolerance test (GTT), hemoglobin A1c (HbA1c), or fasting plasma glucose (FPG) according to ADA guidelines. Screening approaches were compared using Cohen's Kappa (κ) coefficient.
Result(s)
DM and pre-DM were diagnosed by GTT in 3 (4.8%) and 11(17.7%) of subjects, respectively. Screening with FPG and HbA1C failed to identify 100% of DM subjects. GTT and HA1c had only slight agreement ($\kappa = 0.075$)
Conclusion (s)
Women with PCOS should be screened for Pre-DM and DM using GTT. Fasting plasma glucose levels and HA 1c were suboptimal predictors of DM in our cohort.

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Endocrine Disruptors

P903

Correlational evaluation of inflammatory biomarkers in polycystic ovarian disease: a case control study

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Introduction
Contrary to the high prevalence of polycystic ovarian syndrome (PCOS) amongst reproductive age group women, there is disproportionate uncertainity over its etiopathogenesis. Substantial evidence suggests immunological-inflammatory role in causing this endocrine disorder. In this context, we set out study the role of inflammatory biomarkers in PCOS.
Material and methods
This prospective case-control study was conducted on PCOS patients diagnosed based on Rotterdam criteria). Institutional ethical committee approval was obtained. Exclusion criteria were women with galactorhea, hyperthyroidism, any systemic disease that affects their reproductive physiology, or any medication which interferes with the normal function of the hypothalamic-pituitary-gonadal axis. Serum samples were collected from 150 PCOS women and 150 age matched healthy controls. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF-α) and high sensitive C reactive protein (hsCRP) levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.
Results
The mean hSCRP levels was higher in 34% of PCOS woman and its level were 7.9 ± 0.05, 9.9 ± 0.04, 9.9 ± 0.6 and 12.3 ± 0.7 among PCOS (normal weight, obese and over weight) and control subjects respectively. 32% of PCOS women showed raised TNF-α levels and its mean were 159.3 ± 21.3, 302.0 ± 28.9, 202.7 ± 42.5 and 120.0 ± 14.7 among the PCOS (normal weight, obese and overweight) and controls respectively. There was no significant difference among the normal as well as the overweight patients (P value > 0.05), while the levels differed significantly between obese PCOS and controls (P value < 0.05). The IL-6 levels were considerably increased in all the PCOS cases, with the highest in over weight PCOS women. The IL 6 levels differed significantly between the groups (P value < 0.05).
Conclusions
This study shows that there is notable association between inflammatory markers – IL-6, TNF-α and hsCRP with obese PCOS. Intermarker correlation shows positive link between hsCRP and IL-6. The biomarkers appears to predict the metabolic dysfunction in asymptomatic women.
Keywords: Polycystic ovarian disease, Tumour necrosis factor, Interleukin-6, Metabolic dysfunction, Obesity

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P904

Tumor growth of breast cancer was enhanced by fludioxonil, an antifungal agent, via estrogen receptor-dependent pathways

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Previous studies suggest that environmental factors such as high levels of meat consumption, caffeine, cigarette smoking, pesticides, and endocrine disrupting chemicals (EDCs) may enhance the risk of breast cancer. The fludioxonil is an antifungal agent used in agricultural applications and present at measurable amounts in fruits and vegetables. In this study, the effects of fludioxonil on cancer cell viability and migration ability were examined in MCF-7 and T47D breast cancer cell with estrogen receptors and MDA-MB-231 breast cancer cell without estrogen receptors. The MCF-7, T47D and MDA-MB-231 cells were cultured with 0.1% DMSO (control), 17β-estradiol (E_2; 1×10^{-9} M), or fludioxonil (10^{-5}–10^{-8} M). As results, in MTT assay for 9 days, E_2 as a positive control markedly increased MCF-7 and T47D cell viability about 3.5 times and 2.2 times, and fludioxonil (10^{-5} M) also increased cell viability about 1.2 to 1.5 times compared to control. When the respective treatment was co-treated with ICI 182,780, an ER antagonist, MCF-7 and T47D cells viability were reversed to the level of control. However, the cell viability of MDA-MB-231cells was not changed by treatment of fludioxonil and co-treated with ICI 182,780, as did E_2. In the migration assay for 48h, MCF-7 cells and T47D cells were migrated to low chamber from upper chamber via to 0.8 μm pore. And migration of MCF-7 cells and T47D cells by E_2 or fludioxonil were inhibited by co-treatment of ICI 182,780. Although, the cell number of migration in MDA-MB-231 cells by treatment of E_2 or fludioxonil were not had the significance of result compare with 0.1% DMSO including co-treatment of ICI 182,780. These results imply that the fludioxonil may have breast cancer progression effect by increasing cell viability and migration via estrogen receptor dependent pathway. Therefore, we will have to confirm the molecular mechanism for support the change of cell viability and cell migration. And, based on this result, we will identify the mechanism related with estrogen receptor and PI3K/AKT pathway *in vitro* and confirm their effect by using xenografted or orthotopic mouse models in which MCF-7 or T47D cells are subcutaneously injected or are injected into mammary fat pad for 90 days.

Key words: Endocrine disruption; cell cycle gene; cell migration; fludioxonil; breast cancer; estrogen receptor pathway

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P905

Treatment with pesticides, fenhexamid and cyprodinil, resulted in an increase of cell cycle- and metastasis-related genes in an estrogen receptor-dependent pathway in cellular and xenografted mouse models with MCF-7 breast cancer cell

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Fenhexamid (Fen) and cyprodinil (Cyp) are antifungal agents used in agricultural applications. In this study, to examine the effects of two-pesticides on cancer cell viability and metastasis via estrogen receptor pathway, the ER positive-MCF-7 and ER negative-MDA-MB-231 breast cancer cells were used. MCF-7 and MDA-MB-231 were cultured with 0.1% DMSO (control), 17β-estradiol (E_2; 1×10^{-9} M), Fen (10^{-5}–10^{-7} M), Cyp (10^{-5}–10^{-7} M) in the absence or presence of ICI 182,780 (ER antagonist). As results, in MTT assay, two-pesticides increased MCF-7 viability about two times compared to control like E_2 (about 3.5 times). But, when the respective treatment was co-treated with ICI 182,780, MCF-7 cell viability was maintained at the control level. However, MDA-MB-231 cell viability was not affected by E_2 or two-pesticides compared to control. In colony formation assay, MCF-7 cells did form the colony by treatment of E_2 and antifungal agents, but MDA-MB-231 cells did not form. However, E_2 and antifungal agents in the presence of ICI 182,780 did not induce the formation of MCF-7 colony. To examine the morphology change, MCF-7 and MDA-MB-231 cells were incubated on E_2 and two-pesticides in the absence or presence of ICI 182,780. As a result, morphology of MCF-7 cells was changed sharper by E2 and two-pesticides than control or group of co-treated with ICI 182,780. However, morphology of MDA-MB-231 cells by E2 and two-pesticides or co-treatment of ICI 182,780 was the same compared with control. In wound-healing scratch assay, the scratched distance was reduced by MCF-7 cells treated with E2 or two-pesticides compared with control. However, the scratched distance by MCF-7 cells co-treated with ICI 182,780 and MDA-MB-231 cells treated with E_2 or two-pesticides were maintained to the level of control. In migration assay, MCF-7 cells treated with E_2 or two-pesticides migrated more than 5 times compared with control and co-treatment with ICI182,780 inhibited migration of MCF-7 cells. The migration ratio of MDA-MB-231 cells by E2 or two-pesticides was similar to control. These results imply that the two-pesticides may have cancer progression effect by increasing cell viability and migration via ER dependent pathway. Based on this result, we will identify the mechanism related with metastasis of two-pesticides via ER pathway and confirm their effect by using xenografted mouse models in which MCF-7 cells are subcutaneously injected or are injected into mammary fat pad.

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P906

Relationship of urinary bisphenol A to metabolic and hormonal profile in PCOS women

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Objectives
Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women. Its increasing prevalence is probably related to environmental estrogens exposure, such as bisphenol A (BPA). BPA is considered to play an important role in the ethiopathogenesis of PCOS and can be responsible for various clinical symptoms. Aim of the study was to compare the levels of urinary BPA between PCOS women and healthy controls and to assess the relationship of BPA to sexual steroid hormones and metabolic parameters in the PCOS group.
Subjects and methods
Study included 86 Caucasian women with PCOS (age 28.5 + 5.1 years, range 19–43) and 32 controls (age 24.9 + 4.4, range 21–35 years). All subjects were examined for urinary BPA, sex steroid hormones and parameters of glucose and lipid metabolism.
Results
PCOS women had significantly higher BPA than controls (6.1 + 0.786 μg/g creatinine vs 1.65 + 1.2 μg/g creatinine, $P=0.0035$). BPA positively correlated with age ($P=0.01$; $R^2=0.1$), SHBG ($P=0.05$; $R^2=0.07$) and negatively with estrone ($P=0.005$; $R^2=0.12$), DHEAS ($P=0.033$; $R^2=0.18$) and free androgen index (FAI) ($P=0.05$; $R^2=0.08$), respectively. Other steroid hormones (testosterone, free-testosterone, androstenedione, estradiol) and metabolic parametres (BMI, glucose, insuline, HOMA-IR, total cholesterol, LDL, HDL and triacylglycerols) did not show any significant relations. When divided PCOS women into two subgroups according to BPA levels (group with normal BPA and group with elevated BPA, cut off value = 2.14 μg/g creatinine), there was found a significantly higher serum estrone (153.9 + 25.0 pg/ml vs 88.0 + 20.0 pg/ml; $P=0.05$) and FAI (13.23% + 1.7 vs 7.56% + 1.7; $P=0.029$) in the group with normal BPA, and higher SHBG (38.26 + 9.8 nmol/l vs 65.63 + 9.6 nmol/l; $P=0.046$) as well as insulin (10.46 + 1.8 mIU/l vs 15.2 + 1.5 mIU/l; $P=0.05$) in the group with elevated BPA.
Conclusion
We conclude that PCOS patients have higher urinary BPA levels than healthy controls. Increased urinary BPA is related to lower levels of some steroid hormones, such as estrone, DHEAS and FAI, indicating a possible suppressive efect of bisphenols on steroidogenesis.

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P907

Cross hormone therapy in transgender individuals: changes in lipid profile and other cardiovascular risk factor

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Background
Cross-sex hormone therapy (CHT) is known to lead to alterations in cardiovascular risk factor(CVRF).
Objective
To assess changes in lipid profile and other CVRF in transsexual subjects receiving CHT.
Materials and methods
Retrospective longitudinal study. We evaluated individuals with gender identity disorder following CHT, assisted in the Gender Identity Unit from 2015 to 2017.

Primary endpoint was lipid profile change from baseline at 24 months. Secondary endpoints included change in body mas index(BMI), weight, blood pressure(BP) and glycaemic parameters.Statistical analysis was performed with SPSS Statistics 20.0:t-Student to compare means for paired quantitative data and Chi-square for qualitative variables.
Results
40 transsexuals, 19 male-to-female (MtF: 47.5%) and 21 female-to-male (FtM: 52.5%). Mean age 23.86±11.25 years, mean duration of CHT 24.7±39.9 months.Mean age and mean duration of CHT was similar in both group. In the MtF group,weight and BMI increased significantly, from 72.12±19.04 to 75.17±19.96 kg ($P=0.01$) and from 23.84±5.79 to 25.02±5.85 kg/m^2 ($P=0.02$),respectively, as well as diastolic blood pressure(DBP)(from 71.80±15.59 to 75.60±14.72 mmHg ($P=0.03$)) and triglycerides(TG)(from 102.90±83.69 to 108.81±88.37 mg/dl ($P=0.035$). FtM transsexuals also presented an increase in weight(70.02±11.14 to 72.17±11.17 kg ($P=0.02$) and BMI (from 24.03±4.04 to 25.32±4.11 kg/m^2 ($P=0.035$)).No significant differences in lipid profile and blood pressure were observed in this group.Even though final levels were all within normal range.No significant differences were observed with regard to gender (MtF vs. FtM).
CONCLUSION
MtF transsexuals experienced alterations in weight, serum lipid profile and diastolic BP because of CHT while FtM only experience changes in weight and BMI, although final levels were all within normal range. No significant differences were observed with regard to gender (MtF vs. FtM).We suggest that clinicians should monitor glucose and lipid metabolism and blood pressure regularly according to established guidelines.

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Endocrine Nursing

P908

Patient perspectives on sexuality in hypopituitarism

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Aim
The aim of the study was to explore patient perspectives on sexuality in hypopituitarism.
Background
Hypopituitarism usually leads to a complete loss of sex hormones and the condition has a negative impact on sexuality. Previous research has mainly focused on erectile functioning in men and fertility issues in women but little is known about their sexual wellbeing and experiences of hypopituitarism in relation to sexuality.
Design
An interpretative, qualitative methodology inspired by Gadamer's philosophical hermeneutics was carried out.
Methods
Individual interviews were conducted with 19 men and women with hypopituitarism. Data were collected between October 2011 and April 2012.
Findings
Four themes emerged that describe experiences of an altered sexuality in hypopituitarism: Desire, fatigue and lack of initiative, Intimate relationships and love, lust for life and self-perception and a public and private silence surrounding sexuality.
Conclusions
The altered sexuality included sexual functioning as well as wellbeing, which affected both self-perception and intimate relationships. The patient perspective on sexuality in hypopituitarism extends well beyond sexual functioning into issues of sexual wellbeing, intimate relationships, self-perception and cultural, gendered, norms. Nurses can aid patients in adapting to an altered sexuality but current health care practices focusing on sexual functioning and reproduction alone are insufficient.

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P909

Testosterone replacement: 'The best practice'

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Testosterone deficiency syndrome (TDS) may well contribute to a number of co-morbidities and multitude of symptoms which may affect one's daily activities adversely. TDS prevalence in UK is 5:1000 and certain groups of patient's are at higher risk of TDS, in particular elderly and patients with diabetes mellitus where 42% are known to have TDS. A retrospective audit was carried out to bench mark our practice in line with a publication of a recommended National/European guidelines of 'A practical guide for the management of men with suspected testosterone deficiency'. We obtained and analysed the medical records of 35 patients who attended our endocrine services over a 6 month period. 31 of them had already been started on testosterone from the year before. Seven patients were excluded due to lack of data availability. The age in our cohort ranged from 31 to 72 years with a mean age being 53 years. Initial testosterone and PSA results ranged between 0.4 and 9.4 nmol/l (normal 8.4–28.7 nmol/l) with mean of 5.9 nmol/l and 0.1 μg/l to 2.1 μg/l (normal 0–3.0 μg/l) with a mean of 0.7 μg/l respectively. We found the time lapse between initial blood results and testosterone initiation were from 1 to 18 months, with a mean of 7 months. The guidelines suggests; prior to testosterone initiation PSA and a rectal examination (PR) should be carried out. Within our patient group only 5/28 (18%) had a PR, 21/28 (75%) had PSA, 16/28 (57%) had ultra sound scan (USS) of prostate and 16/28 (57%) of our patients have had neither a PR nor an USS. 18/28 (64%) of the patients who had been started on testosterone were on Nebido 1g injection, 15 of whom had this administered by their GP, the other 3 by the hospital Endocrine Specialist Nurse (ESN). The 3 ESN treated patients had an USS before commencing treatment. Recommended on-going monitoring of 3–6 monthly intervals in the first year was achieved on 23/25 (92%) of our patients.
Conclusion
We recommend a dedicated andrology service and a shared care pathway with community colleagues to ensure all patients have received the best possible care by means of investigations, treatment and follow up care in line with National/European guidelines.

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Endocrine tumours and neoplasia

P910

Resveratrol inhibits DHT-induced metastasis of prostate cancer through interfering with the AR and CXCR4 pathway

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Prostate carcinoma is one of the most common malignancies and the second most common cause of cancer-related deaths in men world-wide and is affected by the action of dehydrotestosteron (DHT) via androgen receptor (AR). Resveratrol as a phytochemical in grapes and red wine has diverse effects such as anti-inflammation, anti-oxidant and anti-cancer. CXCR4 as a chemokine receptor has been found to be upregulated in cancer metastasis and has been used as a prognostic marker in various types of cancer, including leukemia, breast cancer, and prostate cancer. In this study, we focused on the role of DHT in the induction of prostate cancer progression by affecting the AR and CXCR4 pathway. Also, we investigated the inhibition effect of resveratrol on DHT - induced prostate cancer metastasis. In cell viability assay, DHT increased the cell viability of LNCaP prostate cancer cell on the other hand, resveratrol and its combination with bicalutamide (BCT) as an AR-antagonist or AMD3100 as a CXCR4 inhibitor significantly reduced the cell viability promoted by DHT. Trans-well migration assay and wound healing assay represented the similar results with cell viability assay. According to the results of tunnel assay, the apoptotic activity was induced by treatment of resveratrol. As results of western blot analysis, the expression of AR, CXCR4, and the downstream genes related with epithelial-mesenchymal transition (EMT) were decreased and the expression of the apoptosis-related genes was increased by treatment of resveratrol and its combination with BCT or AMD3100. This study would suggest that resveratrol and its combination with AR and CXCR4 antagonists can be used in order to suppress the metastatic behaviors of prostate cancer.

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Female Reproduction

P911

Assessment of insulin resistance in polycystic ovary syndrome: HOMA, QUICKI and McAuley indices have only moderate correlation with OGTT-based belfiore index

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Backgroud
Though insulin resistance (IR) is common in polycystic ovary syndrome (PCOS), there is no agreement as to what surrogate method of assessment of IR is most reliable.
Aim
We compared methods based on measurements of fasting insulin and either fasting glucose (HOMA-IR and QUICKI), or triglycerides (TAG) (McAuley index) with insulin resistance (Belfiore) index (IRI) derived from glucose and insulin during a 75-g oral glucose tolerance test (OGTT).
Subjects and methods
Glucose (G) and insulin (I) were measured during OGTT in 478 patients with PCOS (Rotterdam criteria). IR indices were calculated according to the formulae: HOMA-IR = [G] (mmol/l) × [I] (μU/ml)/22.5, QUICKI = 1/[log(I) + log(G)]; while IRI = 2/[(INSp x GLYp) + 1], where INSp, GLYp = insulinaemic and glycaemic areas during OGTT. McAuley index was calculated as Mffm/I = e [2.63–0.28 ln (I) – 031 ln (TAG)].
Results
There was a significant ($P<0.001$), but modest correlation between IRI and HOMA ($R=0.582$), IRI and QUICKI ($r=-0.580$), and IRI and McAuley index ($r=-0.614$). In contrast, there was an excellent correlation between HOMA-IR and QUICKI ($r=-0.999$, $P<0.001$), and HOMA & McAuley index ($r=-0.849$, $P<0.01$). Concordance between HOMA-IR and IRI was poor for subjects with HOMA-IR or IRI above 75th and 90th percentile i.e. those most insulin resistant. In particular, only 53% (70/132) women with HOMA-IR > 75th percentile had IRI value also above 75th percentile, while only 44% (24/54) of women with HOMA above 90th percentile, also had IRI value above 90th percentile. This discrepancy was even more striking for comparison between IRI and McAuley index, where 121/126 (96%), and 52/53 (98%) women with IRI above 75th, and 90th percentile had the value of McAuley index below 75th and 90th percentiles, respectively.
Conclusions
Significant number of women with PCOS can be classified as being either insulin sensitive, or insulin resistant depending on the method applied, with the greatest discrepancies existing for comparison of between IRI (Belfiore) and McAuley indices. Clinical application of surrogate indices for assessment of IR in PCOS must be therefore viewed with an extreme caution.

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P912

Presence of antiphospholipid antibodies is associated with increased failure rates of assisted reproductive techniques: a meta-analysis

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Introduction
The presence of antiphospholipid antibodies is associated pathogenically with thrombotic vascular events and resulting pregnancy complications. Studies support that antiphospholipid antibodies (aPL) impair female fertility by interfering with endometrial decidualization and implantation. This meta-analysis aims to determine the prevalence of aPL in women undergoing assisted reproductive techniques (ART) for in Vitro Fertilization and Embryo Transfer (IVF-ET).
Material and methods
A systematic review of the literature was performed in PubMed regarding observational studies which reported prevalence of aPL among women undergoing ART for IVF-ET and implantation rate was included in their outcome. Studies included women failed to conceive and control women who conceived. A prospectively registered with structured search strategy was employed. The extracted data (patients' and control characteristics and outcomes) were transferred in a standardized form. Risk of bias was assessed by employing Newcastle-Ottawa Score and meta-analysis was performed only if the design of the studies were similar enough for data to be pooled together.
Results
Our systematic review yielded 14 studies, evaluating 3462 women of reproductive age. The prevalence of aPL among women experiencing IVF failure was compared with its prevalence among women who conceived following IVF (4 studies) or with matched women of reproductive age (11 studies). All results consistently showed significantly higher levels of aPL among women experiencing IVF failure. Our results were heterogeneous, due to differences in study designs and inclusion criteria. However, all included studies presented consistent results, supporting our protocol hypothesis.
Conclusion
These results strongly suggest that the presence of antiphospholipid antibodies in women ART for IVF-ET may reduce the rate of the implantation compared to controls and consequently impair the fertilization rate and pregnancy outcome.

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P913

Association between anthropometric parameters and lipid and carbohydrate profiles and CRP as inflammation indicator in women with polycystic ovary syndrome

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Polycystic ovary syndrome is associated with lipid and carbohydrate metabolism disorders, leading to obesity and insulin resistance. The aim of the study was to asses the correlation among anthropometric parameters, metabolic markers (lipid and carbohydrate profiles) and CRP as inflammatory indicator in women with Polycystic Ovary Syndrome. The study consists of 43 women diagnosed with Polycystic Ovary Syndrome based on 2003 Rotterdam criteria. The patients were hospitalized in Endocrinology City Hospital in Piekary in 2016-2017. In order to estimate the anthropometric parameters: BMI, BAI, VAI, WHR and WHtR were used. Concentration of total cholesterol (TC), LDL cholesterol, HDL cholesterol, triglycerides (TGC) also glucose, insulin, HOMA-IR, QUICKI index and CRP were taken from the patients' medical records. CRP > 5 was adopted as the anomalous value. Statistically significant value $P \leq 0{,}05$ was assumed. In the examined group the average BMI (kg/m^2) was 28,0 ± 6,9, BAI 32,7 ± 6,4, VAI 1,7 ± 0,8, WHR 0,8 ± 0,1, WHtR 0,6 ± 0,1. The average concentration of TC (mg/dl) was 184,2 ± 40,2, LDL cholesterol (mg/dl) 99,2 ± 34,9, HDL cholesterol (mg/dl) 64,8 ± 20,6, TGC (mg/dl) 101,2 ± 58,3. The carbohydrate profile consisted of average concentration of glucose (mg/dl) 91,2 ± 13,2, insulin (uU/mL) 13,4 ± 10,9, as well as average values of HOMA-IR index 0,3 ± 0,0 and QUICKI index 3,3 ± 1,0. The average concentration of CRP (mg/l) was 3,4 ± 1,6. HDL cholesterol was statistically lower in patients with higher BMI ($P \leq 0{,}05$, $r=0{,}40$), BAI ($P \leq 0{,}05$ $r=0{,}3$), VAI ($P \leq 0{,}05$, $r=0{,}54$), WHR ($P \leq 0{,}05$, $r=0{,}25$) and WHtR ($P \leq 0{,}05$, $r=0{,}38$). TGC correlated positively ($P \leq 0{,}05$, $r \geq 0{,}16$) with BMI, BAI, VAI, WHR, WHtR. There were not significant correlation observed among TC, LDL cholesterol and studied variables. Fasting glucose and insulin correlated positively ($P \leq 0{,}05$, $r \geq 0{,}23$) with BMI, BAI, VAI, WHR and WHtR. Women with higher value of HOMA-IR index had statistically higher BMI ($P \leq 0{,}05$, $r=0{,}45$), BAI ($P \leq 0{,}05$, $r=0{,}27$), VAI ($P \leq 0.05$, $r=0{,}46$), WHR ($P \leq 0{,}05$, $r=0{,}40$) and WHtR ($P \leq 0{,}05$, $r=0{,}46$). There was negative correlation ($P \leq 0{,}05$, $r \geq 0{,}33$) between anthropometric parameters and the value of QUICKI index. Positive correlation ($P \leq 0{,}05$, $r \geq 0{,}23$) between CRP concentration and BMI, BAI, VAI, WHR and WHtR was observed in the examined group of women. Anthropometric parameters are functional indicators of carbohydrate and lipid metabolism disorders, (except TC and LDL cholesterol concentration) in PCO-S women. High BMI, BAI, VAI, WHR and WHtR might imply an inflammation in the examined group.

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P914

The risk of cardiovascular diseases in relation to anthropometric parameters and CRP concentration in a group of women with polycystic ovary syndrome

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Polycystic Ovary Syndrome increases the risk of cardiovascular diseases. To factors predisposing to cardiovascular diseases belong: hypertension, lipid and carbohydrate profiles, smoking and reduced physical activity. The aim of this study was to determine the association between selected factors predisposing to cardiovascular diseases and anthropometric parameters and CRP concentration in women with Polycystic Ovary Syndrome. The study was conducted amongst 43 women, aged 18-39, diagnosed with Polycystic Ovary Syndrome based on the 2003 Rotterdam criteria. The patients were hospitalized in Endocrinology City Hospital in Piekary in 2016-2017. The selected factors predisposing to cardiovascular diseases (CVD) were: blood pressure different from 135/85mmHg, total cholesterol > 200mg/dl, LDL > 135mg/dl, HDL < 50mg/dl, triglycerides > 150mg/dl, HOMA-IR > 1,5, glucose > 100mg/dl, BMI > 24,9, smoking and reduced or very reduced physical activity and assigned 1 point for every existed factor. Body composition was measured with TANITA BC-420 Analyzer. The results were used to signify the anthropometric indicators (BMI, BAI, VAI, WHR, WHtR). To establish the statistical relationship statistically significant value $P \leq 0.05$ was accepted also to verify the power of correlation between two chosen variables r-Pearsona coefficient was used. Selected factors predisposing to CVD have been recognized in 90.7% of examined women, including at least 4 factors in 22 women. Positive correlation was observed between BAI and predisposing CVD factors ($P \leq 0.05$, $r = 0.35$), as well as between VAI and predisposing CVD factors ($P \leq 0.05$, $r = 0.26$), WHR and predisposing CVD factors ($P \leq 0.05$, $r = 0.38$), also WHtR and predisposing CVD factors ($P \leq 0.05$, $r = 0.46$). Higher numbers of predisposing CVD factors is connected to higher CRP concentration ($P \leq 0.05$, $r = 0.22$). The correlation between predisposing CVD factors and BMI (kg/m^2) was observed ($P \leq 0.05$, $r = 0.45$). Anthropometric parameters as well as CRP concentration are useful tool in determining the risk of cardiovascular diseases in women with Polycystic Ovary Syndrome.

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P915

Experience of managing primary hyperaldosteronism (HP) during pregnancy

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PH during pregnancy is a rare entity with no standardized practice management guidelines available. We report a case of a Latin American 40-year-old patient, with a history of arterial hypertension first diagnosed during her first gestation followed in Ecuador. She presented at 24 weeks' gestation with a fetal demise and high blood pressure, being diagnosed of severe preeclampsia. Cesarean section (CS) was performed. No further control of blood pressure after delivery was reported. Three years after she was referred to our unit at 10 weeks' gestation because of severe hypertension. She was treated with labetalol 600 mg and nifedipine 60mg reporting an optimal arterial blood pressure control until 38 weeks' when a CS was performed. The newborn was a male weighing 2850 g with good perinatal outcome. During her postpartum hospitalization hypertensive peaks and a hypokalemia was observed and treated with valsartan 320 mg and amlodipine 10 mg. PH was diagnosed with a confirmatory test of renin-aldosterone stimulation with furosemide-standing. An adrenal computed tomography (CT), demonstrated a left adrenal node, 20 mm in diameter. Catheterization was not required and treatment with spironolactone 100 mg/daily was started with an optimal control. Adrenalectomy was recommended but it was postponed since she became pregnant again. We visited her at 6 weeks' gestation. We decided to continue treatment with spironolactone at high doses (100 mg/daily) with the consent of the patient until week 20 and reduced the dose to 50 mg/daily due to the possible reported side effect of decrease placental flow. Labetalol 400mg/daily was added to keep blood pressure under optimal control. A CS was performed at 40 weeks' gestation. A female newborn was obtained, weight 3160 g, Apgar 9/10. At follow up, an uncomplicated laparoscopic adrenalectomy was performed, and no further antihypertensive treatment was needed.

Conclusion

Despite the few cases described in the literature, in our experience the treatment with spironolactone at high doses during the first half of gestation allowed a correct management of the blood pressure and probably had a role in preventing preeclampsia with no malformations or adverse effects perinatal. In our case, we didn't choose eplerenone, since the patient was already on spironolactone at time of consultation, was a female fetus and the lack of literature on eplerenone prenatal safety. However eplerone may be recommended in planned gestations to avoid the possible feminizing effect of spironolactone scarcely reported.

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P916

Beneficial effect of *Ecklonia cava* extract in Letrozole-induced polycystic ovary syndrome rats

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Polycystic ovary syndrome (PCOS) is an endocrinal disorder afflicting women mainly during their childbearing age. The symptoms of PCOS are irregular menstrual cycles, weight gain, subfertility, and infertility. However, since the etiology is as yet unclear, the management and treatment are still not well established. Recently, natural substances have been used for PCOS therapy. *Ecklonia cava* is a well-known natural substance that attenuates inflammation, allergy and cancer. In this study, we investigated the effects of *Ecklonia cava* extract in PCOS rats. When Letrozole-induced PCOS rats were exposed to the *Ecklonia cava* extract, the regular estrus cycle was restored, similar to that in placebo rats. Hormone levels, including testosterone, estrogen, LH, FSH and AMH, recovered to their normal states. Histological analysis revealed that the polycystic ovary symptoms significantly decreased in the *Ecklonia cava* treated rats, comparable to normal ovaries. At the transcriptional and translational levels, Cyp19a1, Ar, Esr1, *Esr2* and aromatase were remarkably increased in the *Ecklonia cava* treated PCOS rats than those of Letrozole-induced PCOS rats. These results suggest that *Ecklonia cava* extract inhibits the symptoms of polycystic ovary syndrome through regulating imbalanced hormonal levels and irregular ovarian cycles in Letrozole-induced female rats.

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P917

The paracrine endometrium expression in women with autoimmune thyroid imbalance and spontaneous abortion

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Context

Autoimmune thyroid pathology can lead to serious complications of pregnancy and can be combined with generalized autoimmune imbalance, in particular, in the endometrium. The imbalance in the regulation of the immunocompetent cells activity and the increase of cytokines production are one of the reasons for the failed implantation or disruption of embryo development with future consequences

Objective

To assess the role of paracrine factors (expression of autoantibodies against cytokine receptors IL-1 alpha, IL-2, TNF-alpha, interferon-gamma) in the endometrium in women with autoimmune thyroid diseases and misscariages.

Methods

Immunohistochemical endometrium study was performed on the immunostimulator Leica Bond-Max (Leica Microsystems, Germany). The expression value of markers IL-2 receptor, IL-1α, TNFα, INF-γ was performed using mouse/monoclonal antibodies (Santa Cruz Biotechnology). The immunohistochemical reactions were assessed by a quantitative score method for immunointensity of 0 to 3 (0 - negative; 1 - weak; 2 - moderate; 3 - strong). For reliability of the differences was used Spearman's nonparametric rank correlation method. Statistically significant differences were considered for $P < 0.05$.

Patients

84 women, considering pregnancy, divided into 4 groups: 1- women with reproductive losses and hypothyroidism as outcome of Hashimoto disease, $n = 21$,

mean age - Me 34 [30; 37], 2- $TPOAb^+$ positive women with a history of reproductive losses, $n=21$, mean age - Me 33 [30; 38], 3- women with reproductive failures without autoimmune thyroid disease, $n=21$, mean age - Me 30 [26; 35], 4- healthy women of the control group, $n=21$, mean age - Me 29 [27; 34].
Main outcome Measures
In comparative analysis in all 4 groups was negative expression of IL- 1 alpha and IL-2/CD 25 ($P>0,05$). Significant differences in the expression level of IFN gamma were observed in glands in the group with hypothyroidism and $TPOAb^+$ positive women ($P=0,06$ and $P=0,001$ respectively) than in control group. Furthermore, a negative correlation of expression TNF alpha was observed between the group of women with autoimmune thyroid pathology and women with misscariage and normal thyroid function.
Results
In the course of the research work was revealed an increased level of IFN expression in the group of women with with both hypothyroidism and $TPOAb^+$ positive women.
Conclusion
Expression of IFN gamma is helpful to assess the risk of a possible complication of pregnancy in women with autoimmune thyroid disease, but further research is required. Supported by Grant of President of Russian Federation ND MK-4717.2012.7

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P918

Young lean women with evidence of both premature adrenarche and pubarche display a metabolic, hormonal and psychologic profile that is similar to that of their peers with polycystic ovary syndrome

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Context
The early activation of adrenal *zona reticularis,* denoted by increased circulating levels of adrenal androgens before the age of eight years in girls is called premature adrenarche (PA), while the concomitant appearance of pubic hair is termed premature pubarche (PP). Girls with PA-PP display an unfavorable metabolic, hormonal and psychologic profile, compared to their normal peers and are also at an increased risk of developing polycystic ovary syndrome (PCOS) features peripubertally, especially those born small for gestational age. The natural history of these girls with PA-PP post puberty is unclear.
Aim of the study
To define the metabolic, hormonal, and psychologic profile of young lean women with a history of both PA and PP, born with a normal birth weight. These women were prospectively followed since childhood, did not seek medical assistance and their majority did not fulfill PCOS criteria.
Participants
21 PA-PP women (age: 21.35 ± 3.36 years, BMI: $23.59\pm4.40 kg/m^2$) were compared with 26 controls and 45 women with classic PCOS. Only three women (14%) in the PA-PP group had PCOS by the Rotterdam criteria.
Results
PA-PP women had significantly lower serum total cholesterol (165 ± 20 *vs.* 187 ± 28 mg/dl), LDL (87 ± 21 *vs.* 21 ± 12mg/dl) and higher HDL (65 ± 11 *vs.* 56.2 ± 10.9mg/dl) than controls. Insulin resistance index HOMA-IR was similar in PA-PP (2.09 ± 1.42) and PCOS (2.08 ± 0.83), and significantly higher than that of controls (1.13 ± 0.49). Serum delta 4-androstenedione levels (ng/ml)did not differ between PA-PP (3.22 ± 1.44) and PCOS (3.54 ± 1.14) but were significantly higher than controls (0.58 ± 1.42). Similar findings were obtained for DHEAS and 17OHP, however serum testosterone and free androgen index were comparable among all groups. Ovarian volume (cm^3) was similarly increased in PA-PP (11.14 ± 3.34) and PCOS (10.99 ± 4.61) compared to controls (6.74 ± 1.83). Regarding their psychologic profile, PA-PP women had a significantly higher score of state and trait anxiety, as well as of depressive and eating disorder symptoms than controls, with a pattern that was quite similar to that of PCOS.
Conclusions
Young lean women with a history of PA and PP displayed hormonal, metabolic and psychologic profiles similar to those of their peers with classic PCOS. These findings indicate that in women with PA-PP history, a thorough evaluation and long-term monitoring is needed.

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P919

Endometrium steroid receptors expression in women with autoimmune thyroid pathology and reproductive failures

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The complex study of the endometrium, in particular, immunohistochemical (IHC), allows to determine the state of steroid receptivity and allows to choose the optimal way of examination in women with autoimmune thyroid diseases and miscarriages.
Aim
To evaluate IHC expression of steroid receptors (ERα, ERβ, PR) in endometrium in women with a history of reproductive loss and autoimmune thyroid diseases
Materials and methods
The study involved 63 women with a history of reproductive failures, divided in 3 groups: I ($n=21$) - primary hypothyroidism in the compensation stage, II ($n=21$) - $TPO-^+$ positive patients, III ($n=21$) - without an autoimmune thyroid pathology. The control group ($n=21$) included women planning pregnancy. The endometrium IHC expression of receptors for estradiol and progesterone in stromal and glandular cells was performed using mouse/ monoclonal antibodies to ERβ, ERα, PR (Leica, Germany). As an evaluation of immunohistochemical reactions was used AllRed Score evaluation method
Results
Was found the expression decrease of ERα in stroma in I and II groups compared with III ($P<0.001$ and $p=0.002$, respectively) and the control group ($P<0.001$). A lower expression level ERα in glands was observed in I and II groups, compared to III ($P<0.001$ and $p=0.03$, respectively) and IV ($P<0.001$). The ERα expression in stroma and glands between groups III and IV were not statistically different ($p=0.513$ and $p=0.07$, respectively). In the analysis of progesterone receptors, a significant increase in the expression of ERβ in stroma and glands was found in group III in comparison with IV ($P<0.001$). In addition, lower rates of ERβ expression in groups I and II were found, but statistical significance was confirmed only in women with primary hypothyroidism ($P=0.04$). The results of PR expression in stroma and glands indicated their decrease in the I group in relation to the remaining cohorts (PR stroma: $P<0.001$, PR of the gland: $p=0.03$).
Conclusions
The estimation of steroid receptors endometrium expression indicated a high degree of damage to the receptor apparatus in women with autoimmune thyroid diseases with imbalance of the secretory function of the endometrium glands. Early diagnosis of the combined immune disorders in this cohort of patients and the proper pre-gravity training will ensure greater effectiveness in the management of subsequent pregnancies.

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P920

Does Crohn's disease have an effect on female fertility?

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Introduction
Impaired fertility in women with Crohn's disease compared to healthy women seems to be a consequence of Crohn's disease, according to older studies. However, data are not consistent, and it is not clear why could the reduced fertility occur. Influence on ovarian reserve might be one of the answers.
Patients
The study group consisted of women with Crohn's disease. The control group consisted of age and BMI matched healthy women with no history of assisted reproduction.
Methods
All patients completed a personal questionnaire, focused on fertility parameters as well as the Crohn's disease phenotype, activity and treatment. Ovarian reserve was measured by the serum concentration of anti-mullerian hormone (AMH).

In patients with Crohn's disease, we investigated the effect of the Crohn's disease phenotype and prior treatment on the ovarian reserve.
Results
We included 50 women with Crohn's disease and 50 controls. Comparing two groups, we did not observe any difference in rates of birth, spontaneous abortion, contraceptive use and age of menarche. Serum AMH was not different between the groups (3.026 vs. 3.19, $P=0.74$), 54 vs. 52% of women had an optimal ovarian reserve (AMH >2.27), and 23.7 vs. 19.23% had low ovarian reserve (AMH <0.68), with no difference. Age was the strongest parameter affecting decline of the ovarian reserve, with not difference between patients with Crohn's disease versus controls. We did not detect any significant impact of disease duration, type of disorder, inflammatory activity, or type of treatment on the rate of age-related AMH decline. However, we found a more pronounced age-related AMH decline in patients with prior IBD surgery compared to no surgery (slope -0.12 versus -0.29, $P=0.04$) and the trend towards the more pronounced decline in L2 colic phenotype compared to L1 and L3 (slope -0.33 vs. -0.14, $P=0.12$). Finally, women older than 30 years had a more pronounced age-related AMH decline if Crohn's disease lasted for more than 5 years (slope -0.31 vs. -0.2, $P=0.029$).
Conclusion
We found that women with Crohn's disease as compared to controls had the same ovarian reserve and equal rate of its age-related decline. More pronounced age-related decrease in ovarian reserve was observed in women with prior IBD surgery and those over 30 years of age with Crohn's disease lasting for more than 5 years. In these cases, patients may be advised not to delay a pregnancy.

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P921

Effects of food restriction on estrous cycle and leptin hormone in mongolian gerbils (*Meriones unguiculatus*)

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Reproductive systems of the Mongolian gerbils are controlled by the photoperiod but body weight is independent of photoperiod. Food intake has an effect on reproduction and gerbils are very sensitive about food intake. Leptin hormone has controls on both food intake and body weight. Finding a link between changes in feeding behavior and reproductive activity in relation to obesity-related issues will play an important role. In this study, three groups were established; a) food was introduced as ad libitum, b) food was introduced only in dark period, c) food was introduced only in light period. Daily food consumption and weekly body weights were calculated. Estrus cycles have been observed by means of vaginal smears every day and preparations were photographed. Leptin measurement at each phase of the estrus cycle phases was evaluated separately. When all groups were compared in terms of food consumption, the control group was higher ($\sim$6.34 g/day) than in other groups however, other groups were found to be similar ($\sim$4.53 g/day). It was found that the weight variations of the three groups were similar. The leptin value in diestrus phase of both food restricted groups was higher ($\sim$24 ng/ml; $P<0.05$) than the control. The values in proestrus stage were similar ($P>0.05$), but the values in estrus stage had higher leptin when the animals were fed in the dark phase ($\sim$32 ng/ml; $P<0.05$). Leptin in metaestrus stage was lower in the group fed in the light phase but other groups had similar leptin values ($\sim$7 ng/ml; $P<0.05$). 4-day estrus cycles of the control group were prolonged in food-restricted groups ($\sim$7–8 days). As a result, feeding behavior has led to changes both in leptin values and in the estrus cycle. Since the relationship between nutrition and leptin in recent years is important in terms of obesity, changes in feeding rhythm may directly affect on the organism's reproductive system.

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P922

Amenorrhea and high intensity training

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Introduction
Functional hypothalamic amenorrhea (FHA) is one of the most common causes of secondary amenorrhea. There are three types of FHA: weight loss-related, stress-related, and exercise-related amenorrhea. The latter is fairly common among competitive athletes. Currently the Olympic Committee includes amenorrhea in the "Relative Energy Deficiency Syndrome in Sport (RED-S)". The syndrome of RED-S refers to impaired physiological function including metabolic rate, menstrual function, bone health, immunity and cardiovascular health caused by relative energy deficiency. Admission to the Military Academy is a period of intense physical exercise where trainees are at risk for amenorrhea and consequently RED-S.
Objectives
To verify the prevalence of amenorrhea in high intensity training included in a military set and to identify possible predictors.
Material and methods
Observational, descriptive, cross-sectional and retrospective study of female soldiers who entered the Military Academy from 1992 to 2016. A questionnaire was formulated to analyze variables before admission (demographic data, sports federation, gynecological history, use of oral contraceptives (ACO)) and variables after admission (period in amenorrhea, sports injuries). Descriptive and statistical analysis was performed using the chi-square test.
Results
102 military personnel answered the questionnaire. At the time of entry, they had an average of 18.8 (17-25) years and 36.2% were federated in a sport. 37.3% took ACO, of the remaining 64 cadets, 43.8% (28/64) had menstrual dysfunction, and 35.9% (23/64) presented amenorrhea, on average 5 months. 78.3% recovered spontaneously, 17.4% resorted to ACO and 4.3% to other therapies. Of de total, 39.2% suffered injuries, and there was no difference between the group taking ACO, the group that had amenorrhea and the group without amenorrhea. No difference was found regarding previous sports history.
Discussion and conclusions
The prevalence of amenorrhea in women subjected to high intensity physical training (characterized in this study by military training) was 35.9%, and it was not possible to correlate it with previous sport history or with the presence of injuries. Studies show prevalence of amenorrhea in runners and dancers range from 20 to 66%, revealing that this condition is very common. However, investigations should include assessment of systemic and endocrinologic etiologies, as FHA is a diagnosis of exclusion.

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P923

Detection of SRY gene in patients with turner syndrome

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Background
The presence of the Y chromosome and Y-specific sequences (e.g: *SRY*, DYZ1, DYZ3, DYS132, *ZFY,* and *TSPY*, etc) in Turner syndrome patients is a risk factor for gonadal tumors (mostly gonadoblastoma) in dysgenetic gonads. Unfortunately approximately 60% of gonadoblastoma cases, there is a potential to progress towards invasive germ cell tumors (mostly dysgerminoma). Girls with Y chromosomal material also present a higher risk of virilization, because the stroma cells and granulosa/Sertoli cells present in the dysgenetic gonad can produce androgens. Therefore, TS patients Y chromosomal material should undergo prophylactic gonadectomy. In this study we aimed to share our clinical experience.
Methods
The SRY gene was investigated in 71 of 85 TS cases (aged 0.3 months-27 years) between 2005 and 2017. Fluorescent *in situ* hybridization (FISH) was used until 2014, after then SRY gene analysis was performed by polymerase chain reaction (PCR). In 25 cases with used FISH method, SRY gene analysis was investigated second times by PCR method.
Results
Pathologic findings were not found in terms of virilization, clitoromegaly, posterior labial adhesions in case of TS. SRY gene was found to be negative in all cases. Further studies did not require due to no pathologic findings normal over visualization in USG.
Conclusion
Routine testing for SRY or the presence of Y chromosome material in TS patients without masculinization is not clinically warranted. For these reasons, molecular screening to detect Y-chromosomal sequences is currently recommended in TS individuals with masculine features who are negative for Y material by conventional cytogenetic and FISH analyses. In these individuals, multiple sequences adjacent to the Y centromere should be amplified using PCR.

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P924

Time-dependent regulation of kisspeptin/Kiss1R and TAC3/TACR3 systems expression in human ovarian granulosa cells from polycystic ovary syndrome (PCOS) patients and non-PCOS patients

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The kisspeptin/Kiss1R and tachykinin 3 (TAC3)/tachykinin receptor 3 (TACR3) system in the hypothalamus are essential for reproduction. Recent study suggested that the two peptide systems are both expressed in the ovary, particularly in the granulosa cells. The expression profile of the two systems in human granulosa cells has not been fully investigated yet. We collected the granulosa cells from normal infertile control patients and patients diagnosed with PCOS in Peking University Third Hospital. The expression of *Kiss1*, *Kiss1R Tac3*, and *Tacr3* increased at 2000 when compared with 1000 in granulosa cells from normal control patients. While the expression of *Kiss1* and *Tacr3* increased, *Kiss1R* and *Tac3* decreased at 2000 when compared with 1000 in patients with PCOS. HCG had no significant effect on the expression of Kiss1, Kiss1R Tac3, and Tacr3, but significant promoted the expression of circadian time gene PER1. Kisspeptin-10 and Tacr3 antagonist, senktide decreased the expression of circadian gene *Bmal1* and *per2*, but it was not statistically significant. The expression of Kiss1 was related to the expression of *Bmal1* at different time within a day. Our results suggest that ovarian kisspeptin/Kiss1R system and Tac3/Tacr3 system have a different expression profile in patients with and without PCOS. The discrepancy may be related to the different circadian clock gene expression manner in the granulosa cells.

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P925

Hyperandrogenism in a postmenopausal woman:A clinical challenge

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Introduction
Hyperandrogenism is an uncommon finding in postmenopausal women. Possible sources of the elevated androgen levels include Cushing's syndrome, Polycystic ovarian syndrome, benign and malignant androgen secreting ovarian tumors, ovarian hyperthecosis, adrenocortical tumours and iatrogenic hirsuitism.
Case
A 65 year-old lady was referred with a raised testosterone level of 2.6 nmol/l [0–1.8 nmol/l]. She experienced weight gain and fatigue for over 6 months. She also had nail changes and hair loss, with increased hair growth on her face and acne that had gradually worsened in the last year. There were no changes to voice or muscle size. She experienced menopause in 2003 and received HRT therapy for a year then stopped it. Clinically she scored 15 on Ferriman Gallway score for hirsutism with no clinical features of Cushing's syndrome or Acromegaly.
Investigations
Testosterone of 2.7 nmol/l [0–1.8 nmol/l], Androstenedione 3.1 nmol/l [<3.0 nmol/l], LH 42.4 mIU/ml, FSH 104.0 mIU/ml, DHEAS 0.9 umol/L, Oestradiol<90, Prolactin 91 mU/l, 17-hydroxyprogesterone Progesterone < 1.6 nmol/l, Insulin growth factor-1: 25.6 nmol/l, overnight dexamethasone suppression test: Cortisol <25, TSH 0.71 mU/l [0.35–5.5 mU/L], T4 13.6 pmol/l [10.0–19.8 pmol/L]. Ultrasound pelvis showed a bulky right ovary. MRI pelvis was unremarkable with no worrying features. DEXA scan showed normal bone density. A CT adrenal scan showed a mildly nodular appearance to the left adrenal gland, however, there were no focal adrenal lesions. GnRH agonist suppression test: GnRH agonist administration resulted in a dramatic decline in testosterone levels with Testosterone level of 0.5 nmol/l, Androstenedione of 2.2 nmol/l, LH 1.4 mIU/ml, FSH 7.8 mIU/ml on the 4th week following the injection. There was dramatic improvement of her symptoms. She has now been referred for oophorectomy.
Discussion
Identification of the source of elevated androgens often creates a clinical challenge. Hyperandrogenism has virilizing physical effects but is also associated with dyslipidaemia, hypertension, insulin resistance, uterine and cardiovascular disease. If the source is identified, surgery (whether oophorectomy or adrenalectomy) is often curative. Medical management with GnRH agonist/analogues or antagonists has been reported in the literature but may have associated side effects.

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P926

Polycystic ovary syndrome and insulin-like growth factor (IGF) system.

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Objectives
Insulin-like growth factors 1 and 2 (IGF1 and IGF2) are widely expressed mitogenic peptides playing a role in the fetal developement and differentiation. Evidence suggest their possible involvement in the pathogenesis of metabolic syndrome and probably in polycystic ovary syndrome (PCOS).
Aim
Aim of the study was to assess the relationship of serum IGF1, IGF2 and IGF binding protein 3 (IGFBP3) levels to steroid hormones and metabolic parameters in PCOS women.
Subjects and methods
The study included 56 Caucasian women diagnosed with PCOS (age 28.62±5,2 years, range 19-43). All patients were examined for parameters of glucose and lipid metabolism, sexual steroid hormones and serum IGF1, IGF2 as well as $IGFBP_3$ levels.
Results
Nonobese PCOS women had higher IGF1 than those with BMI>25 with borderline significance (211±15.6 v.s. 160.7±16, $P=0.06$). No significant differences in serum IGF2 and $IGFBP_3$ levels in women according to BMI have been detected. IGF1 negatively correlated with HOMA IR ($R^2=0.23$, $P=0.03$), waist circumference ($R^2=0.15$, $P=0.045$) and triacylglycerols ($R^2=0.23$, $P=0.02$), but not with sexual steroids. On the other side $IGFBP_3$ was in positive correlation with TAG ($R^2=0.22$, $P=0.0215$), total cholesterol ($R^2=0.2$, $P=0,028$), LDL cholesterol ($R^2=0.2$, $P=0.03$), dihydrotestosterone ($R^2=0.14$, $P=0.049$) and estrone ($R^2=0.21$, $P=0.014$). Neither correlation between serum IGF2 and metabolic variables nor between IGF2 and steroid hormones have been detected.
Conclusion
We conclude that higher IGFBP3 level is more related to metabolic parameters and steroid hormones in PCOS women than both serum IGF1 and IGF2. Further studies are needed.

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P927

Disentangling polycystic ovary syndrome (PCOS) components by liquid-chromatography – tandem mass spectrometry (LC-MS/MS) steroid profiling

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Introduction
Clinical and laboratory hyperandrogenisms indistinctly contribute to PCOS diagnosis; however, they differ in hormonal and metabolic correlates and require proper therapeutic strategies. Circulating biomarkers of hirsutism were not identified so far, with elevated testosterone being observed only in half of hirsute patients. Reasons for such inconsistencies possibly relies in previously used immunoassays, nowadays recognized as not adequate because of poor reliability and limited steroid panel. The present study aimed at defining the circulating steroid fingerprint that specifically distinguishes hirsutism by LC-MS/MS profiling of a broad steroid panel.
Methods
Sixteen serum steroids were determined in 352 patients (age 14–49 years) in follicular phase. The independent effect of ovarian dysfunction (OD; oligo-amenorrhea and/or PCO morphology), hyperandrogenemia (testosterone≥1.56 nmol/L and/or androstenedione≥5.72 nmol/L) and hirsutism (modified-Ferriman-Gallway score≥8) on circulating steroids was valued. Moreover, hirsute ($n=74$) vs not-hirsute ($n=47$) women were compared within patients showing both OD and hyperandrogenemia.
Results
OD directly associated with LH ($P=0.048$) and LH/FSH ($P<0.001$), and negatively with FSH ($P<0.001$). OD positively associated with androstenedione ($P=0.002$), 17OHprogesterone/progesterone ($P<0.001$), 17OHprogesterone/17OHpregnenolone ($P=0.004$), androstenedione/dehydroepiandrosterone

($P<0.001$), and negatively with progesterone ($P=0.026$), dehydroepiandrosterone ($P=0.029$), dehydroepiandrosterone-sulfate ($P=0.034$) and 11deoxycortisol/17OHprogesterone ($P=0.003$). Hyperandrogenemia positively associated with mFG-score ($P=0.012$), ACTH, LH and LH/FSH (all $P<0.001$), insulin ($P=0.025$) and HOMA-IR ($P=0.045$). Hyperandrogenemia positively associated with 17OHpregnenolone, progesterone, dehydroepiandrosterone, 17OHprogesterone, estrone (all $P<0.001$), dehydroepiandosterone-sulfate ($P=0.004$), dihydrotestosterone ($P=0.009$), corticosterone, 11deoxycortisol, cortisol (all $P<0.001$), cortisone ($P=0.009$), 17OHprogesterone/progesterone ($P<0.001$) and androstenedione/dehydroepiandrosterone ($P=0.014$), and negatively with dehydroepiandrosterone-sulfate/dehydroepiandrosterone, testosterone/androstenedione, estrone/androstenedione, estradiol/testosterone, dihydrotestosterone/testosterone and cortisol/11deoxycortisol (all $P<0.001$). Hirsutism directly associated with BMI ($P=0.014$) and inversely with HDL ($P=0.041$). Hirsutism also associated with lowering progesterone ($P=0.007$) and 17OHprogesterone ($P=0.003$) and increasing androstenedione/17OHprogesterone ($P<0.001$) and 11deoxycortisol/17OHprogesterone ($P=0.021$). Compared with not-hirsute, hirsute women with OD and hyperandrogenemia exhibited higher BMI ($P=0.002$) and dehydroepiandrosterone/17OHpregnenolone ($P=0.011$), and lower SHBG ($P=0.001$), 17OHprogesterone ($P=0.030$), testosterone ($P=0.004$), androstenedione/dehydroepiandrosterone ($P=0.024$) and testosterone/androstenedione ($P=0.039$).

Conclusions

Androstenedione excess in OD apparently originates by gonads, as indicated by imbalanced gonadotropin, low progesterone, increased 17hydroxylase activity and reduced adrenal secretion. Hyperandrogenemia is featured by insulin resistance, combined ovarian and adrenal hypersecretion of the overall steroid profile, and reduced precursors' conversion in downstream active steroids. Hirsutism is characterized by obesity and dyslipidemia, by low 17OHprogesterone and, in the PCOS context, by mild hypertestosteronemia and reduced SHBG, overall suggesting that this phenotype could result by increased free-androgens at the pilosebaceous unit.

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P928

Anxiety and depression in patients with polycystic ovarian syndrome

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Background

Polycystic ovary syndrome (PCOS) occurs in women of reproductive age and is characterized by hyperandrogenism, polycystic ovaries, oligomenorrhea or amenorrhea. Estimated prevalence is at least 6.5%. Women having PCOS tend to be overweight or obese. In addition to endocrine, metabolic and gynecological, features of PCOS, a number of psychological problems add up which affect quality of life and psychological well-being in women with PCOS.

Materials and methods

Case-control study conducted from July 2017 to January 2018 at ABSTH Gujrat after ethical approval from IRB. Non-probability consecutive sampling was used. 50 patients having PCOS were included in study and compared to 50 healthy subjects after their consent. Clinical characteristics of PCOS were compared in both groups. Assessment of anxiety and depression was done using DSM-V criteria. Statistical analysis was done using SPSS 20.0.

Results

Mean age was $26.16+5.54$ and $25.48+6.27$ years, mean weight $72.26+16.53$ and $64.7+13.51$ kg and mean BMI was $28.96+5.87$ and $24.55+5.24$ kg/m^2 in cases and controls respectively. Hirsutism (72% vs 18%), oligomenorrhea or amenorrhea (98% vs 12%), hypertension (28% vs 6%), weight gain (50% vs 12%) , heaviness of voice (12% vs 6%), enlargement of clitoris (16% vs 6%), hair fall (74% vs 34%), acne (68% vs 16%) and hyperglycemia (4% vs 0%) were compared in both groups. Presence of hirsutism, oligomenorrhea or amenorrhea, hypertension, weight gain, hair loss and acne were significantly associated with PCOS ($P<0.05$). BMI was independent risk factor for development of anxiety ($P=0.001$) and depression ($P=0.000$). Relative risk of anxiety in cases was 3.3333 (95% CI, 0.9751–11.3954) while that of depression was 5.1667 (95% CI, 2.3652–11.2863). Depression was significantly associated with PCOS ($P<0.001$) but anxiety was not significantly associated ($P=0.055$).

Conclusion

Depression is significantly present in patients with PCOS as compared to healthy women with BMI as independent risk factor.

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P929

A retrospective analysis of the audiometric data of a cohort with turner syndrome

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Turner Syndrome (TS) is a multi-systemic genetic condition in females caused by partial or complete deletion of one X chromosome. It affects approximately 25-50 per 100,000 live births. Recent data shows that up to 60% of patients with TS will experience recurrent otitis media and 30% will suffer permanent hearing impairment. International guidelines recommend audiometric screening at diagnosis, every three years in childhood and at least every five years in adulthood for TS patients. In this retrospective review we aimed to assess the patterns of hearing loss with formal audiometric analysis in a cohort of adult females with confirmed TS attending a tertiary referral centre. Of three patients only nine (16.7%) had unimpaired hearing. A total of 24 patients had some hearing abnormality and one patient failed to attend for assessment. The majority of patients ($n=18$) had a sensorineural hearing loss pattern. Only one patient displayed solely conductive hearing loss and five patients had a mixed pattern. Mean age of patients with hearing loss was $39.3+10.6$ years (versus $35.1+12.6$ years in the total population and $23.7+7.4$ years in the population with normal hearing). This is in keeping with the known natural history of TS where recurrent otitis media leads to eventual cochlear damage as the patient gets older. Patients with hearing loss were also more likely to have cardiac abnormalities (45.8% vs 22%; $P=0.67$) and thyroid function abnormalities (50% vs 44%; $P=0.77$) than TS patients with normal hearing profiles. Of the patients with normal hearing one patient had a 45XO karyotype and the remaining eight were all mosaic karyotypes. In the group with hearing impairment four patients had 45XO karyotype, twelve had mosaic patterns and the remainder had an unknown karyotype. Of 16 patients referred for hearing aids two patients declined them. In conclusion, greater awareness is needed among physicians regarding the prevalence, severity and prognostic implications of hearing impairment in patients with TS.

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P930

The relationship between uric acid levels and metabolic parameters in patients with polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is a common, multifaceted endocrinopathy associated with metabolic alterations such as insulin resistance, hyperinsulinemia, dyslipidemia, and obesity, and thereby an increased risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Endothelial dysfunction and chronic inflammation are early findings in the atherosclerotic process. Elevated serum levels of uric acid may reflect low-grade chronic inflammation. But there are controversial data whether increased the uric acid level in PCOS patients. This study was aimed to examine the relationship between uric acid, lipoprotein levels and insulin resistance in obese and non-obese patients with PCOS.

Methods

Eighty-three young women with PCOS were included this study. Plasma levels of glucose, insulin and uric acid were measured. The patients were divided into two groups according to a cut-off BMI value of 30 kg/m^2. Anthropometric variables, hormonal and metabolic profiles were evaluated in both groups. Insulin resistance was evaluated by homeostasis model assessment (HOMA-IR).

Results

A total of 83 premenopausal PCOS patients with ($n=37$, mean (s.d.) age: 24.3 (4.7 years) or without obesity ($n=46$, mean (s.d.) age: 29.4 (6.3) years) were included in this study. Plasma uric acid levels and HOMA-IR were significantly higher in women with obese PCOS patients than non-obese PCOS patients. Serum fasting total cholesterol and hemoglobin A1c levels were similar between obese and non-obese groups. Compared with non-obese PCOS subjects, obese PCOS subjects had high HOMA-IR, insulin, TG and uric acid levels. Plasma fasting glucose levels, postprandial glucose levels and androgen levels were similar between obese and non-obese women with PCOS.

Conclusion

Our findings revealed significantly higher levels for plasma insulin and HOMA-IR values in obese PCOS patients when compared to non-obese PCOS patients. Obesity is the main determinant of serum uric acid concentrations in PCOS

patients. Measurement of serum uric acid could help the detection of insulin resistance and related disorders in patients with PCOS.

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P931

Pure leydig cell tumor of the ovary in young premenopausal female

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Background
Leydig cell ovarian tumors (LCOT) represent a rare type of sex-cord stromal tumors accounting for less than 0.1% of all ovarian tumors. (1) Although rarely described in young, LCOT most commonly occur in postmenopausal women (2). The prominent clinical features of LCOT are rapidly progressive virilization, recently described, secondary erythrocytosis and OSA (3). Suppressed plasma leptin has also been reported in patients with LCOT (4), however direct correlation of leptin with testosterone level is still debatable.
Clinical case
A 42-year old woman, presented for evaluation of hirsutism. Past medical history was significant for hypothyroidism, type 2 DM, obesity class II, OSA and secondary amenorrhea that started after the birth of her child at age 20. Previous biochemical studies demonstrated elevated testosterone leading to diagnosis of PCOS. Physical examination showed virilization, frontal alopecia, facial plethora, laryngeal hypertrophy, hirsutism (Ferriman-Gallwey score of 35), truncal obesity, acanthosis nigricans, and clitoromegaly. Laboratory studies revealed elevated total testosterone of 1242 ng/dl ($<$ 70 ng/dl), low normal estradiol of 40.6 pg/ml (11.0–462.1 pg/ml), suppressed LH and FSH, normal prolactin, 17-OH progesterone, 24 urine free cortisol, DHEA-S, and TSH. The patient had marked erythrocytosis (Hgb of 18.3 g/dl (11.2–15.7 g/dl) and hematocrit $>$53% (34.1–44.9%), and significant insulin resistance ($>$100 units of insulin a day and four other oral hypoglycemics; HOMA-IR 11.2). Furthermore, she had elevated fasting serum insulin of 57.1 uIU/ml (normal:2.6–24.9 uIU/ml), HgbA1C 9.7%, and suppressed serum leptin level of 4.2 ng/ml (14.1–78.4 ng/ml). Pelvic ultrasound and CT of abdomen and pelvis with intravenous contrast did not reveal an adrenal adenoma or pelvic mass. Ovarian vein sampling was considered, however patient elected for TAH-BSO. Intra-operatively, both ovaries were normal in appearance. Pathology revealed 3.4 cm right ovarian pure Leydig cell tumor. Postoperatively, serum testosterone, Hgb/Hct levels rapidly normalized. Nine months after the surgery, plasma leptin increased to 39.7 ng/ml (22–121 ng/ml).
Conclusion
Secondary erythrocytosis and OSA in premenopausal women, when associated with markedly elevated testosterone levels, warrant further investigation and a high degree of suspicion for LCOT. Furthermore, in this case study, we re-demonstrated that extremely high testosterone has a suppressive effect on leptin production, as reflected by circulating levels of this hormone, which normalized following the resection of the tumor, without significant changes in BMI. The mechanism of this effect remains to be elucidated.

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P932

Effect of maternal smoking on steroidogenesis

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Objective
Smoking during pregnancy could have impact on steroidogenesis, with more marked changes in smokers carrying boys as well as in their newborns. The aim of study was compared steroid hormones between non-smokers, ex-smokers, which stop smoking in the beginning of pregnancy, and active smokers.
Method
We focused on changes in steroidogenesis in the blood of mothers in their 37th week of pregnancy and in mixed cord blood from their newborns. Because of difference in steroid hormones due to sex of fetus, it is necessary to analyze separately results according the fetus sex. We included 47 healthy women carrying female fetuses with physiological pregnancies (22 non-smokers, 11 active smokers and 14 ex-smokers). The group of women carrying male fetus were excluded due to low numbers in the subgroups. Seventeen steroids were measured by LC-MS/MS method.
Results
We found higher androstenedione in smokers and ex-smokers compared to non-smokers at the 37th week. We found no changes in the female newborns.
Conclusion
Smoking during pregnancy, but unfortunately also stop smoking in the beginning of pregnancy, induces changes in the production of steroids in the mother. Stop smoking is required, but much earlier could bring more benefit.

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P933

Fertility restoration in female patients with hypopituitarism

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Hypopituitarism is relatively rare disorder characterized by different kind of pituitary deficit, and GH-deficiency as well as hypogonadotropic hypogonadism (HH) are the most often met ones. The prevalent cause of hypopituitarism is organic lesion of hypothalamo-pituitary region (pituitary tumors, craniopharyngiomas, empty sella turcica and etc). Successful neurosurgery and optimal replacement hormonal treatment allow patients to appeal to a doctor about pregnancy. Results of fertility restoration in 22 patients with hypopituitarism were compared in this study. Women 22–34 y.o. with duration of HH from 2 to 10 years were observed: 4 patients with isolated HH, 12 – with other adequately treated pituitary deficiencies. Before ovulation stimulation patients were treated with 17β-estradiol (2–4 mg) and dydrogesterone (10–20 mg) in sequence manner no less than for 12 months, this period was used for restoration of physiological endometrium function, increase of uterus volume, correction of treatment of other pituitary deficits (if needed). AMH levels were normal in 19 women and low in 3. In eight women there were 16 stimulations of superovulation according to standard 'long' or 'short' IVF protocols (group 1), 1–8 eggs were obtained per protocol. In other 8 women there were 12 ovarian stimulations using human recombinant gonadotropins with individualised dose titration (group 2), 1–3 ovulated follicles were usually observed per stimulation. In more 8 women (including 2 with previous unsuccessful ovarian stimulation) 12 mild stimulations of ovulation according to individualized IVF protocols were done (group 3), 1–3 eggs per protocol. Individual approach for groups 2 and 3 included: pre-treatment for 2–3 months with low (37.5 MU) rFSH doses in case of low number of antral follicles, estrogen treatment continuation during ovarian stimulation, addition of rLH to rFSH from 6–7 day of stimulation in case of retardation of follicle growth. Moreover, in group 3 GnRH agonists/antagonists were not used because spontaneous LH surge were not expected. Total doses of gonadotropins used for ovarian stimulation were same or below in groups 2 and 3 compared with group 1. During pregnancy replacement treatment of accompanying pituitary deficits were correlated. Rates of 'take-home-baby' were 56.25%, 66.67% and 66.67% accordingly. Main reasons for failure were other infertility factors (male, immunological, concurrent gynaecological). Thus, modern assisted reproductive technologies can help patients with hypopituitarism to restore fertility but individualized approach is highly recommended taking into account both assisted reproductive technologies features and hypopituitarism points. Pregnancy attainment in a woman with hypopituitarism is real ART of medicine.

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P934

The inflammatory markers and central obesity in policystic ovary syndrome

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The waist-to-height ratio (WHtR) has recently gained attention as an anthropometric index showing the highest predictive value for cardiometabolic risk in PCOS and healthy women. Central adiposity is the key driving force behind a constellation of inflammatation linked to insulin resistance, metabolic syndrome and cardiovascular diseases. PCOS is also considered to be linked to chronic inflammatory processes. Platelet count ratio/mean platelet volume (PLT/MPV), lymphocyte–white blood cell count (L/WCC) and neutrophil to lymphocyte ratio (NLR) are the useful markers of the detection of systemic inflammation. Our aim was to investigate PLT/MPV, L/WCC, NLR, high-sensitive C-reactive protein (hsCRP), ferritin, lipid profile (cholesterol, LDL, HDL, TG) and insulin resistance index (HOMA-IR) in 265 patients with PCOS and with or without central obesity classified according to WHtR levels. PCOS was diagnosed according to Rotterdam criteria. A WHtR cutoff of 0.5 was used as an universal cutoff for central obesity in adults. Therefore 156 low-WHtR and 88 high-WHtR PCOS patients were included in the study. High-WHtR patients had statistically higher WBC, PLT, PLT/MPV, NLR, ferritin and CRP levels ($P > 0.05$, nonparametric Mann-Whitney test). Cholesterol, LDL and TG levels and HOMA-IR were also higher in high-WHtR PCOS patients. L/WCC was lower in high-WHtR vs. low-WHtR PCOS patients. There was positve correlation between PLT/MPV and CRP, cholesterol, LDL, TG levels and HOMA-IR in all PCOS patients. NLR positively correlated with CRP, LDL, TG and ferritin level, and HOMA-IR. L/WCC was negatively associeted with CRP, TG and ferritin level, and HOMA-IR (nonparametric Spearman monotonic correlation test). Central obesity in PCOS patients was associated with WBC, PLT, PLT/MPV, L/WCC and NLR levels. Further prospective studies concerning inflammation, central obesity and PCOS are needed.

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P935

The clinical utility of serum anti-Müllerian hormone (AMH) in patients aged over 40 with their first IVF treatment

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Objective
To evaluate the clinical significance of AMH in predicting IVF outcomes among patients over age 40 undergoing the first IVF cycle.
Design and methods
This is a retrospective study. Patients aged 40 or older who underwent their first IVF cycle from January 2013 to September 2014 in CHA Gangnam fertility center were included ($n = 201$). All patients received gonadotropin-releasing hormone (GnRH) antagonist protocol, with a starting dose of 75–225IU recombinant FSH. Serum samples were collected prior to IVF treatment. Serum AMH level and other patient characteristics were analyzed. The main outcome was total retrieved-oocyte number and clinical pregnancy.
Results
The mean age was 41.8 ± 2.1 years and the mean AMH level was 0.35 ± 0.17 ng/ml. The 76% ($n = 153$) of patients was diagnosed as poor responders, fulfilling the Bologna criteria. There was a positive correlation between serum AMH levels and the number of oocytes retrieved ($R^2 = 0.123$, $P < 0.0001$). 30 out of 201 patients achieved clinical pregnancy (14.9%) and the receiver operating characteristic (ROC) curve analysis for prediction of clinical pregnancy showed that AMH had an area under the curve (AUC) of 0.64. Both day 3 serum FSH and BMI had lower accuracy (AUC 0.50 and 0.43, respectively) than AMH. Furthermore, the optimum cut-off level of AMH was 0.27 ng/ml (sensitivity 93.3%, specificity 42.0%, respectively).
Conclusion
Serum AMH concentration is a promising biomarker for the prediction of the number of total oocytes retrieved and the clinical pregnancy in old aged patients, at the time of their first IVF cycle with GnRH antagonist protocol. The cut-off level of 0.27 ng/ml AMH can be used to predict clinical pregnancy.

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P936

Child wish and fertility preservation in assigned female at birth transgender persons living in Belgium

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Objectives
Gender affirming hormonal and/or surgical care is associated with reduced fertility. Over the last years, the options for transgender persons to fulfill their child wish have increased. Previous research (mainly focused on transgender persons visiting health care professionals) on fertility in transgender persons assigned female at birth (AFAB) shows low fertility preservation utilization. Ideas and concerns of AFAB transgender persons regarding fertility preservation and child wish have never been reported in a large, non-clinical sample.
Materials and methods
An anonymous web-based survey on fertility and parenthood was conducted in Belgium in 2017, which invited all persons aged ≥ 16 years who identified themselves as trans* to participate. AFAB transgender people were selected for this substudy, which included transgender men (TM) and gender non binary (GNB) persons).
Results
The questionnaire was filled out by 426 participants, of which 172 (40.4%) AFAB (141; 68.8% TM and 64; 31.2% GNB). Sixty-one (35.5%) respondents had a current/future child wish. Child wish was fulfilled in 14 (8.1%) and inexistent in 64 persons (37.2%) (other categories: 19.2%). Child wish did not differ between TM and GNB persons ($P = 0.304$). In total, 130 AFAB persons (75.6%; TM: 99; 85.3% and GNB: 31; 55.4%) had previously sought medical help for their gender identity, of which 27 (20.8%) considered the loss of fertility due to the transitioning process undesirable and of which half (75; 57.7%) did not wish for fertility preservation. Of the total AFAB population, 14 people (10.3% - 79 missing, TM: 12; 12.9%, GNB: 2; 4.8%) had frozen germ cells. The top three reasons not to proceed with fertility preservation included not feeling the need for this (52; 54.2%), having to take hormones for follicle development (27; 28.1%) and the price for freezing germ cells (27; 28.1%). Barriers encountered for fulfilling the child wish included: the assumed difficulties in the adoption procedure (38; 41.3%), fear of discrimination against the child (35; 38.0%), fear of being discriminated as a transgender parent (30; 32.6%) and the price for using own genetic material (30; 32.6%).
Conclusion
Although child wish in our AFAB population is comparable to earlier research, we report lower fertility preservation utilization rates, reflecting the barriers transgender persons face when considering fertility options (including the costs and the need to postpone hormone therapy). GNB persons' opinions regarding fertility are assessed here for the first time, showing different needs for gender affirming treatment and fertility preservation.

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P937

Oral glucose tolerance test vs fasting plasma glucose determination for the assessment of glucose metabolism disturbances in women with Polycystic Ovary Syndrome

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Background
Polycystic ovary syndrome (PCOS) is a common endocrine condition in women at reproductive age, in whom, glucose metabolism disturbances are commonly observed. In addition, overweight and obesity, especially visceral obesity, are more prevalent in PCOS women, which enhances the resistance to insulin action,

and as consequence, the onset of impaired glucose tolerance (IGT) and/or type 2 diabetes mellitus (T2DM). Clinical guidelines recommend oral glucose tolerance test (OGTT) in all PCOS patients as a screening tool; however, other authors suggest that this test should only be considered in case of obese patients, older than 40 years, and/or in hyperandrogenemic phenotypes.
Methods
Observational transversal study that included 379 PCOS women, recruited between 1998 – 2017, in whom a 75-gr OGTT was performed for the assessment of glucose metabolism disturbances. Diagnostic agreement was observed between fasting and 120-min glucose concentrations in all patients, and after stratifying them by BMI, age and circulating androgen concentrations.
Results
14% of the patients showed impaired fasting glucose while OGTT detected IGT in 16% of the cases, and T2DM in 2%. When fasting glucose was normal, OGTT detected IGT in 13% of patients, percentage that rose to 50% when fasting glucose was $\geq$100 mg/dl. OGTT detected IGT in 6% of lean patients, 15% when overweight, and 18% in obese women with normal fasting glucose. Hyperandrogenemic phenotypes presented IGT in 14% of the cases, while 10% of non-hyperandrogenemic women showed values $\geq$140 mg/dl. In younger patients ($<$40-year-old) with normal fasting glucose, IGT was present in 13% of them, conversely, in women older than 40 years, glucose concentrations $\geq$140 mg/dl after OGTT was observed in the 66% of the cases who previously had glucose values $\leq$100 mg/dl. Finally, in the 95% of patients with normal fasting glucose values, a normal response after OGTT was observed in younger, non-hyperandrogenemic patients with normal BMI.
Conclusions
OGTT is the method of choice for IGT screening and should be performed in all overweight/obese PCOS women. A fasting glucose determination could detect 95% of pre-diabetic conditions in lean, younger and non-hyperandrogenemic PCOS women.

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P938

Potential toxicity of cefuroxime therapy on rats' ovary

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The aim of the present study was to evaluate the potential toxicity of Cefuroxime (CFR), a second-generation cephalosporin antibiotic, on ovary of 'wistar' rats. A total of 32 adult female rats (12 weeks old) were intraperitoneally injected with CFR at a dose of 0, 30, 60 or 120 mg/kg, divided into two equal doses daily, for 7 days and sacrificed 24 h after the last dose. Biochemical assays showed significant reduction in oestradiol and progesterone levels in comparison with the control group ($P<0.05$). In addition, ovarian levels of reduced glutathione (GSH) and glutathione peroxidase (GPx) activity were decreased in the CFR-treated groups in a dose dependent manner ($P<0.05$). However, ovarian malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) seemed not to be influenced by this drug. In consistance with these results, histological investigation showed that the structure of the ovary was perfectly conserved among CFR-treated rats. In conclusion, CFR induced oxidative stress and disrupt hormonal balance in the rats' ovaries without disturbance of normal structure of ovaries.

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P939

Polycystic ovary syndrome (PCOS) associates with dissatisfied body image and weight loss attempts at age 31 and 46 – A prospective, population-based Cohort study

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Introduction
Being overweight or obese are common characteristic of women affected by polycystic ovary syndrome (PCOS). Indeed, 50–70% of the women are obese and more likely to present with higher growth rate and obesity already from early childhood compared with women without the syndrome. Obesity predisposes women with PCOS to adverse metabolic outcomes such as metabolic syndrome, insulin resistance and diabetes. Recent studies have also revealed a high prevalence of eating disorders and altered body image among women with PCOS, however, population-based data and longitudinal follow-up studies on body image and weight loss attempts are lacking.
Materials and methods
The present study assessed the association of body image and weight loss attempts with PCOS in a prospective, general population-based follow-up birth cohort ($n=5889$ females). Postal questionnaires were sent at age 31 (81% answered) and 46 (72% answered). Women reporting both oligoamenorrhea and hirsutism at age 31 and/or PCO/PCOS-diagnosis by age 46 were considered as having PCOS ($N=280$) whereas asymptomatic women at age 31 or without PCO/PCOS-diagnosis by age 46 comprised a control group ($N=1573$). Questions on body image and weight loss attempts and clinical examinations were performed at ages 31 and 46.
Results
Women with PCOS were more dissatisfied with their weight compared with controls both at age 31 and 46 (72.3% vs 52.4%, $P<0.001$ and 86.4% vs 69.0%, $P<0.001$). PCOS was associated with risk for body dissatisfaction at age 31 and 46 (Odds ratio, OR 2.39, 95% confidential interval, CI [1.691–3.63] and 2.92[1.901–4.476]) and the association remained statistically significant after adjusting for BMI and depression and anxiety score (Hopkins Symptom Checklist-25, HSCL-25) (31 years: OR 1.70[1.026–2.808]) and 46 years: OR 2.67[1.372–5.183]). Women with PCOS were more likely to have weight loss attempts compared with controls at age 31 and 46 (47.1% vs 34.0%, $P=0.001$ and 62.8% vs 47.5%, $P<0.001$, respectively). In regression analysis PCOS associated with weight lost attempts independent of BMI. There was a significant but unexpected weak association between waist circumference (WC) and BMI with weight lost attempts in the whole female population (WC: OR 1.11 [1.093–1.119], respectively and BMI: OR 1.40 [1.351–1.444]).
Conclusions
Women with PCOS were more dissatisfied with their weight compared with controls and they were more likely to attempt to lose weight by age 46. As the differences between the groups were independent from BMI, further studies to elucidate the reasons for body dissatisfaction are warranted.

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P940

Subchronic exposure to kalach 360 SL-induced endocrine disruption in female ovaryrats

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Kalach 360 SL (KL), glyphosate (G) surfactant-based herbicides, is a systemic herbicide effective against weeds. It was applied in agriculture in Tunisia and

throughout the world, which can represent a risk to non-target organisms. The aim of this study was to investigate the morphological and biochemical aspects of ovary injury after exposure to KL. Female Wistar rats were divided into three groups: group 1 was used as a control; group 2 orally received 0.07 ml of KL, (126 mg of G/kg) and group 3 orally received 0.175 ml of KL (315 mg of G/kg) each day for 60 days. The subchronic exposure of KL induces impaired folliculogenesis, ovary development, decreased oestrogen secretion, promoted oxidative stress and impairments of ovary histological aspects. Histological finding shows necrosis cell, vacuolisation of follicles, dissociated oocytes and granulosa cell, associated with several atretic follicles. We conclude that KL induces endocrine disruption and ovary damage in female rats.

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P941

Acute and delayed responses of steroidal hormones after a resistance training session: time-of-day effects.

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The present study aimed to investigate the effect of time-of-days (TOD) on some biochemical and hormonal responses after resistance training sessions.
Methods
Ten trained subjects performed three resistance-training-sessions at 0700 h, 1300 h and 1700 h. Each training-session included six upper and lower body resistance exercises with 3×10 repetitions. Blood lactate (Lac), creatine kinase (CK), lactate dehydrogenase (LDH), cortisol (C) and testosterone (T) were collected at rest, 3min and 48h after each-session.
Results
At rest, steroidal hormones were higher in the morning compared to the evening ($P<0.01$), whereas, no significant TOD effect on Lac, CK or LDH was observed. 3min after training, whatever the TOD, Lac, CK and T increased significantly ($P<0.001$). However, a significant decrease in C and a significant increase of T/C ratio were registered only after morning training. 3 min and even 48 h after training, the diurnal variations (i.e. morning to evening) of CK and C have been altered with higher early evening values of CK and lower one of C; whereas, T, Lac and LDH conserved their resting diurnal variation. Additionally, 48 h after the morning session, CK and T/C ratio remained elevated compared to the baseline levels.
Conclusions
In conclusion, resistance exercises soliciting both lower and upper limbs seems to alter the diurnal variation of CK and Cortisol, to enhance the morning anabolism/catabolism status and to produce more favorable environment for muscular adaptation up to 48 h post-training.

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P942

Recombinant FSH and biosimilars result in different intracellular signaling

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Introduction
Follicle-stimulating hormone (FSH) biosimilars, differing for source cell and glycosylation pattern, are commercially available for therapy of hypogonadism and assisted reproduction techniques (ART). Although these molecules are commonly used in clinical practice, comparison of their action *in vitro* was poorly investigated.
Aim
The aim of the study is to compare recombinant FSH- and biosimilars-induced cell response *in vitro*.
Material and methods
Different batches of FSH and biosimilars were used, i.e. recombinant FSH Gonal-F® (Merck KGaA, Darmstadt, Germany), Bemfola® 150, 300 and 450 (Finox Biotech, Kirchberg, Switzerland) and Ovaleap® 450 and 900 (Teva Pharmaceutical Industries, Basel, Switzerland). Human primary granulosa lutein cells (hGLC), as well as FSH receptor (FSHR)-transfected HEK293 cells were stimulated by increasing doses of FSH or biosimilar (1-100 nM range). Intracellular cAMP and Ca^{2+} production as well as β-arrestin two recruitment were evaluated by BRET. Moreover, CREB and ERK phosphorylation was evaluated by Western blotting analysis. Finally, 8- and 24-h progesterone and estradiol synthesis were investigated by immunoassay.
Results
While no different cAMP and β-arrestin two recruitment were detected in FSHR-transfected HEK293 cells (cAMP EC50 range = 6 ± 0.09 – 19 ± 0.07 ng/ml; β-arrestin two EC50 range = 72 ± 0.27 – 489 ± 0.26 ng/ml; Mann-Whitney's *U* test; $P>0.05$; $n=4$), Ovaleap® induced lower levels of pCREB and pERK1/2 activation than other biosimilars in hGLC (Mann-Whitney's *U* test; $P<0.05$; $n=4$). Kinetics analysis revealed no intracellular Ca2+ increase upon treatment by 4.4 μg/ml Ovaleap® and Bemfola® (Mann-Whitney's *U* test; $P<0.05$; $n=4$), while treatment of FSHR-transfected HEK293 cells by 4.4 μg/ml Gonal-F® rapidly induced intracellular Ca^{2+} peak. In hGLC, FSH and biosimilars induced both 8- and 24-h progesterone and estradiol synthesis, but no differences were found between the EC50s and plateau levels ($n=4$).
Discussion
Preparation-specific intracellular signaling patterns were activated by recombinant FSH and biosimilars, but the downstream steroid synthesis was similar. Especially, biosimilars failed to induce intracellular Ca2+ increase.
Conclusions
Recombinant and biosimilar drugs used in clinical practice as equivalent, are linked to specific intracellular signaling in vitro. Results may be relevant for their use *in vivo*.

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P943

Two cases of Mayer-Rokitansky-Küster-Hauser syndrome type 2 with bilateral inguinal hernia

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Background
Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is defined as aplasia or hypoplasia of the uterus and vagina in female with normal 46,XX karyotype. Isolated congenital absence of the uterus and vagina is classified as MRKHS type 1 (typical form). If it is associated with at least one concomitant congenital malformation that mainly affect the renal and skeletal system, is classified as MRKHS type 2 (atypical form). We report here the cases of MRKH type 2 with inguinal hernia in a child and an adolescent in order to pay attention concomitant malformations for early diagnosis in childhood before the onset of amenorrhea.
Cases
Patient 1: 5-year-old girl was referred to our clinic for the absence of vaginal orifis. She had a history of inguinal hernia repair and operated for atrial and ventricular septal defect in infancy. She had also vesicoureteral reflux. Pelvic ultrasonography and magnetic resonance image (MRI) showed absence of the uterus and vagina. Lumbarization S1 was established as a skeletal anomaly. Patient 2: 15-year-old girl who presented a primary amenorrhea studied with transabdominal and pelvic ultrasonography and pelvic MRI, which demonstrated a complete agenesis of uterus, a functional cyst in the right ovary, and a left pelvic ectopic kidney. She had not a major skeletal anomalies. She underwent bilateral inguinal hernioplasty.
Conclusions
The concomitant malformations contribute to clinical profile heterogeneity of women with MRKHS. Our cases are to show the importance of further investigation in cases of inguinal hernia to diagnose other concomitant anomalies to establish earlier that patients have MRKHS type 2.

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P944

Mayer Rokitansky Küster Hauser syndrome: a case report

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Objective
Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) is a very rare congenital anomaly characterised by vaginal agenesis and a spectrum of different genitourinary tract anomalies. Typical form of this syndrome is characterised by congenital absence of the uterus and upper 2/3 vagina with normal ovaries and fallopian tubes and atypical form of the syndrome is associated with anomalies of the ovaries and fallopian tubes and renal anomalies.
Case report
18 years old patient with symptom of primary amenorrhea was admitted to our hospital. She developed clinical signs of puberty at 13 years old. Physical examination showed an average height and weight (160 cm/54 kilos) and normal breast examination (Tanner 5) and normal axillary and pubic hair. Normal clitoris, labia major and minor were also noted. The USG showed an ectopic right kidney with rotation anomaly and ectopic left kidney which are located in the pelvis, and uterus and ovaries were not found. Biochemical analyses were in normal limit ranges. Hormone profile included Follicular stimulating hormone (4.2 mUI/ml), Estradiol (98 pg/ml) and testosterone (0.2 ng/ml), which were all normal, indicating normal function of the hypothalamic-pituitary-ovarian axis. The karyotype was normal (46, XX). Because of the discrepancy between the clinical and laboratory findings and ultrasound examination, MRI was performed, and confirmed that right and left ectopic kidney and the absence of uterus, nevertheless could not show ovaries.
Conclusion
MRKH atypical form is should be in mind if there are features of its history, physical examination, US and MRI evaluations in a patient with primary amenorrhea.

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P945

Current situation of adult patients with Turner syndrome in Tenerife (Spain)Current situation of adult patients with Turner syndrome in Tenerife (Spain)

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Introduction/ objectives
Turner syndrome (TS) comprises a group of sex chromosomal abnormalities of heterogeneous clinical presentation. During the infant period, the pediatric endocrinologist coordinates their follow-up and it is important to ensure its continuation during the adult stage. The objective of this study is to know the current clinical situation, occupational, educational, social and medical monitoring of patients affected TS in Tenerife.
Material and methods
Retrospective study of the clinical parameters evaluated during the follow-up in consultation of the patients affected with TS in our center ($n=19$). Telephone interview in which demographic data, employment and educational status, current health and medical follow-up were asked.
Results
Age 36.3 ± 9.2 years. Karyotype: mosaicism (47.4%); 45X0 (52.6%). All patients were treated with growth hormone (GH): age of onset 10.1 ± 4.1 years, dose 40.2 ± 9.5 μg/kg per day; duration 6.5 ± 2.7 years, bone age of suspension 14.7 ± 0.7 years. Final adult size of 151 ± 7.9 cm. They received treatment with oxandrolone 36.8%. Pubertal induction was performed in 94.7% of patients: age of onset 11.9 ± 0.8 years, bone age of onset 13.4 ± 1.9 years, age of menarche 15.6 ± 2.7 years. Most common disorder: hypogonadism (94.7%), osteoporosis/ osteopenia (52.6%), hypothyroidism (52.6%), obesity (42.1%), dyslipidemia (42.1%), nephrolithiasis (26.3%), hypertension (21.1%), otitis of recurrence (21.1%), congenital lymphedema (21.1%). Clinical follow-up: endocrinology (47.4%), gynecology (31.6%), primary care (21%). Educational level: primary (23%), secondary/ vocational training (38.5%), university (38.5%). Occupationally active (92.3%). Residence: family (61.5%), couple (23.1%), single (15.4%). Couple currently (23.1%) and offspring (10.5%). Lifestyle: ex-smokers (21.1%), exercise (30.8%).
Conclusions
The results obtained in our sample of adult final height in patients treated with GH do not differ from the results described in other series. The doses of GH, duration of treatment and age of pubertal induction are adapted to the guidelines of management of patients with TS. The most prevalent pathology is hypogonadism followed by osteoporosis and hypothyroidism. The follow-up is heterogeneous. There is a greater tendency towards parental dependence and absence of a partner.

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P946

Primary amenorrhea due to gonadal gysgenesis in a girl with karyotype 46,XX

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Introduction
Gonadal dysgenesis is a rare cause of primary amenorrhoea, and refers to a number of conditions in which gonadal development is abnormal leading to streak or hypoplastic gonads. We present a rare case of a girl with primary amenorrhea, tall stature, gonadal dysgenesis and karyotype 46,XX. A 15 years old girl with primary amenorrhoea referred to our department for futher investigation. On clinical examination she was tall (height 1.74 m), her weight was 76 kg and BMI 25,10. She had normal intelligence and appearance with no dysmorphic features. External genitalia were normal but was at a prepubertal stage of sexual development. Laboratory investigations revealed hypergonadotrophic hypogonadism (FSH = 77.4 mIU/ml, LH = 42.32 mIU/ml, $E_2=5$ pg/ml), subclinical hypothyroidism (TSH = 5.1 μIU/ml) and hypoplastic uterous and small right ovary on an abdominal ultrasound. Bone age was delayed at 14 years and the karyotype was 46, XX. Hormonal replacement therapy was initiated in the begining with 17β-estradiol alone and then in combination with norethisterone. After nine months on treatment she developed breast and pubic hair (Tanner III and III-IV respectively) and an increased size of uterous and right ovary and visualization of the left ovarian tissue was observed on MRI Pelvis.
Conclusions
46,XX gonadal dysgenesis is a rare cause of primary amenorrhoea. It is important to be diagnosed as early as possible so that HRT treatment begins promptly. The kind of hormone replacement depends on the time of diagnosis and the status of secondary sexual characteristics.

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P947

Hormonal and metabolic differences between hyperandrogenic women with PCOS

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Introduction
Hyperandrogenism (HA) is frequent but not universal characteristic in women with polycistic ovary syndrome (PCOS). According to the ESHRE/ASRM definition, hyperandrogenism criterion could be clinical (hirsutism) and/or biochemical (hiperandrogenemia). The aim of this study was to analyze metabolic and hormonal characteristics among women with PCOS with different forms of hyperandrogenism.
Methods
We analyzed 458 women with PCOS diagnosed using ESHRE/ASRM criteria and divided into three groups: 1) with clinical HA only (PCOS-CHA:N = 67, age: 26.7 ± 5.6 years, BMI: 23.6 ± 5.2 kg/m^2), 2) with biochemical HA only (PCOS-BHA:N = 151, age: 25.5 ± 5.3 years, BMI: 24.5 ± 6.5 kg/m^2), 3) with both clinical and biochemical HA (PCOS-CBHA:N = 240, age: 25.0 ± 5.2 years, BMI: 26.4 ± 6.2 kg/m^2), and 104 healthy controls (age:29.2 ± 5.8 years, BMI: 25.4 ± 16.8 kg/m^2). CHA was defined as Ferriman-Gallwey score ≥ 8, BHA as presence of FAI ≥ 6% and/or testososterone > 2 nmol/l. We measured fasting glucose (FG), insulin, lipids, FSH, LH, testosterone, SHBG, androstenedione, estradiol, DHEAS and 17OHprogesterone, while HOMA-IR and FAI were calculated. Differences between-groups were age and BMI adjusted.

Results
In comparison to controls, PCOS-BHA and PCOS-CBHA had higher total cholesterol (TC) ($P=0.031$ and $P=0.001$, respectively), LH ($P<0.001$ and $P<0.001$, respectively), DHEAS (both $P<0.001$), all PCOS groups had higher triglycerides ($P=0.006$, $P=0.004$, $P=0.001$ respectively), PCOS-CBHA had higher 17Ohprogesterone ($P=0.012$) and PCOS-CHA had higher androstenedione ($P=0.027$). In comparison to PCOS-CHA, PCOS-BHA and PCOS-CBHA had higher LH ($P=0.001$ and $P=0.026$, respectively) and PCOS-CBHA had higher 17OHprogesterone ($P=0.030$) and TC ($P=0.001$). There were no between-groups differences in HOMA-IR, FSH and estradiol. Significant correlations was found among CHA between androstenedione and HOMA-IR ($r=0.33$, $P=0.04$).
Conclusions
PCOS with different forms of hyperandrogenism present with different cardiometabolic risk factors and different hormone profiles. Women with hirsutism and without hyperandrogenemia have less severe metabolic and hormonal status.

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P948

Turner Syndrome and Abnormal liver function

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Introduction
Turner Syndrome (TS) is known to be associated with congenital malformations and a greater incidence of autoimmune disease. Many others organs systems are also affected to varying degrees and at different stages of life such as abnormal liver function. This disease is often detected on routine investigation and is not accompanied by signs or symptoms of liver disease. We report the case of a young Turnerian who presents a disruption of his hepatic balance with a strictly normal etiological investigation.
Case
A 10 years old girl was referred for short stature. Her past medical history was unremarkable. On examination, she had a height of 118 cm (-<3 S.D.). She had a female phenotype with female external genitalia (Tanner stage: stage 1). It presents a universal alopecia. Examination of cardiovascular, respiratory and neurological systems was normal. Hormonal investigations revealed hypergonadotropic hypogonadism with FSH level of 181.4 mIU/ml, LH level of 41 mIU/ml and a estradiol level <9 pg/ml. Pelvic ultrasonography showed a hypoplastic Uterus without visualization of the ovaries. Cytogenetic analysis of peripheral blood revealed a karyotype with 45 chromosome with one X chromosome missing (45, X). And the FISH (*fluorescence in situ hybridization*) analysis showing hybridization of x chromosome centromere probe to normal X and small ring X chromosome in a 46X,r(X) metaphase. Laboratory investigations revealed normal hematological and biochemical parameters except for Alanine aminotransferase (ALT) (87UI/l>45ui/l) and Alkaline phosphatase (AP) (819ui/l> 200ui/l), γ-Glutamyl transferase and serum bilirubin level were normal. Hepatotoxic medications and alcohol was ruled out and we have completed by abdominal ultrasound which showed no hepatic impairment. Viral hepatitis was suspected but the serologies were negative. Otherwise, autoimmune hepatitis was eliminated as the immunological survey showed negative anti-mitochondrial, anti-smooth muscle and anti-LKM1 antibodies. Finally the patient is treated with Ursodeoxycholic acid therapy. The evolution was marked by an improvement in liver function ALT (32ui/l), AST (40ui/l), AP (220 ui/l).
Conclusion
The incidence of biochemical liver abnormalities is frequent and should be investigated in any patient with TS. It appears that this is a benign condition which does not seem to reflect any liver dysfunction. The estrogen-progestin replacement therapy; should not be stopped because of its beneficial effects on the overall quality of life of these patients. Liver involvement in TS patients necessitates appropriate management and follow-up.

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P949

Association of hormonal and metabolic status with carotid intima-media thickness in women with polycystic ovary syndrome

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Introduction
Women with polycystic ovary syndrome (PCOS) have numerous risk factors that lead to higher risk for cardiovascular diseases (CVD) and stroke. Measurement of carotid intima-media thickness (CIMT) is a marker of CVD.
Methods
We analyzed 399 women with PCOS diagnosed using ESHRE/ASRM criteria (age: 25.5±5.1 years, BMI: 24.9±6.2 kg/m^2), and 82 BMI-matched healthy controls (age 29.2±5.9 years, BMI 25.3±8.6 kg/m^2). In follicular phase of menstrual cycle we determined fasting serum fasting glucose (FG), insulin, lipids, CRP, testosterone, SHBG, DHEAS, 17OH-progesterone, androstenedion, estradiol, TSH, fT4, CIMT and blood pressure (BP). HOMA and FAI were calculated. Differencies between groups were age adjusted.
Results
PCOS had higher total cholesterol-TC ($P=0.02$), LDL-C ($P=0.03$), triglycerides ($P=0.02$), HOMA-IR ($P=0.04$), testosterone ($P<0.001$), FAI ($P<0.001$), DHEAS ($P<0.001$), androstenedione ($P=0.02$), 17Ohprogesterone ($P=0.005$), systolic and diastolic BP ($P=0.004$ and $P=0.001$, respectively), and lower HDL-C ($P=0.02$), SHBG($P<0.001$) and estradiol ($P=0.04$). There were no between-group differences in CIMT, CRP, glucose, TSH, fT4. Significant correlations among PCOS were obtained for CIMT and BMI ($r=0.10$, $P=0.04$), triglycerides ($r=0.11$, $P=0.33$), estradiol ($r=-0.14$, $P=0.013$), systolic and diastolic BP ($r=0.13$, $P=0.01$ and $r=0.18$, $P=0.001$, respectively). There were no correlations between androgens and CIMT among PCOS.
Conclusions
Although women with PCOS have higher CVD risk, we did not show differences in CMIT in our PCOS women in comparison to respective BMI matched controls. Overall, there are no associations between CIMT and androgen status or insulin resistance in our examined group of PCOS women.

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P950

Oxidative stress markers in women with polycystic ovary syndrome without insulin resistance

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Introduction
Polycystic ovary syndrome (PCOS) is usually accompanied by abdominal obesity and insulin resistance which are related with low-grade chronic inflammation, as evidenced by elevation of multiple markers of inflammation, among which is oxidative stress. However, as far as oxidative stress presence, the existing data are limited. The purpose of this study was the investigation of several oxidative stress markers in women with PCOS without insulin resistance.
Material and Methods
15 patients with PCOS according to NIH criteria (1990) and 10 women matched for age and BMI, with normal cycles and without clinical or biochemical hyperandrogenemia were studied. Somatometric parameters were recorded and androgen, SHBG, insulin and blood glucose levels were measured after an overnight fast. Free androgen index (FAI) and homeostatic model assessment of insulin resistance (HOMA-IR) were calculated. Among oxidative stress markers, catalase (CAT) and superoxide dismutase (SOD) activity were determined, total antioxidant capacity (TAC), glutathione levels (GSH), lipid peroxidation by thiobarbituric acid reactive substances (TBARS) and nitrogen monoxide (NOx) levels were assessed in peripheral blood. Statistical analysis was performed with logistic SPSS 16.0.
Results
Patients and controls were comparable regarding age, BMI (22.6±2.8 vs 20.5± 2.2 kg/m^2, $P>0.05$) and the level of insulin resistance as expressed by HOMA-IR (2.09±1.0 vs 1.6±0.5, $P>0.05$). As expected, androgen levels were higher while sex hormone-binding globulin levels were lower in patients with PCOS,

compared to control group ($P<0.01$). Oxidative stress as evidenced by lipid peroxidation and TAC was not different in women with PCOS compared to controls. However, a significant increase in CAT and SOD activity was observed, indicating an inner stress- counterbalanced effect ($P<0.01$). CAT activity was positively correlated with total testosterone ($P=0.019$) and D4-androstendione ($P=0.008$) levels, while SOD activity was positively correlated with total testosterone ($P<0.001$), D4-androstendione ($P=0.001$), DHEA-S ($P=0.023$) and glucose ($P=0.02$) levels and negatively with SHBG ($P=0.001$) levels.
Conclusions
These preliminary results show that, oxidative stress is not increased in women with PCOS without insulin resistance, probably due to its sufficient counter-balance by the inner antioxidant response. Insulin resistance may be a factor that is crucially involved in the aggravation of pro-inflammatory oxidative stress.

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P951

Thyroid axis in women with polycystic ovary syndrome

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Introduction
Women with polycystic ovary syndrome (PCOS) often have other comorbidities and one of them is Hashimoto thyroiditis (HT). The aim of the sudy was to analyze metabolic and hormonal status among women with PCOS, with and without HT.
Methods
We analyzed 167 women with PCOS diagnosed using ESHRE/ASRM criteria divided on PCOS with HT ($PCOS_{with}HT$, $N=27$, age: 25.8 ± 5.2 years, BMI: 28.5 ± 7.3 kg/m^2) and without HT ($PCOS_{no}HT$, $N=140$, age: 25.1 ± 4.5 years, BMI: 24.5 ± 5.9 kg/m^2) and also 48 healthy controls (HC) divided on HC with HT (HC_{with} HT, $N=10$, age 32.6 ± 5.4 years, BMI 23.1 ± 3.8 kg/m^2) and HC without HT ($HC_{no}HT$, age 29.7 ± 6.3 years, BMI 23.6 ± 6.2 kg/m^2). In follicular phase of menstrual cycle we determined fasting serum glucose (FG), insulin, lipids, CRP, testosterone, SHBG, DHEAS, 17OH-progesterone, androstenedion, estradiol, TSH, fT4, fT3. HOMA and FAI were calculated. Differencies between groups were age-adjusted.
Results
$PCOS_{with}HT$ had highest BMI than all other groups (28.7 ± 1.2 kg/m^2) and significantly differed from all other groups: vs. $PCOS_{no}HT$ (24.7 ± 0.5 kg/m^2), $P=0.02$; vs. $HC_{with}HT$ (23.1 ± 3.8 kg/m^2), $P=0.02$; vs. $HC_{no}HT$ (23.7 ± 6.2 kg/m^2). There was no difference in any other measured parameter between $PCOS_{with}HT$ and $PCOS_{no}$ HT.
Conclusions
Women with PCOS and HT are more obese than PCOS without HT. However other metabolic and hormonal factors do not differ between examined groups of PCOS women.

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P952

Determinants of fatty liver disease in adult women with Turner syndrome

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Introduction
Turner syndrome (TS), defined by the loss of X chromosome material, affecting 1/2500 females born. Associated with TS are a variety of comorbidities such as obesity and fatty liver disease, many of which increase in prevalence with age. The Turner Syndrome Life Course Project at UCLH has collected data on over 800 women over the last 20 years. Annual health surveillance in our adult TS clinic allows for screening for liver enzymes, such as Alanine Transaminase (ALT), Alkanine Phosphatase (AlKP) and Gamma-glutamyl transferase (GGT). Persistent elevation of liver enzymes may represent a risk for cirrhosis. Here we report regards to on the determinants of fatty liver disease in women with TS.
Methods
An analysis of 8,659 clinic visits from 829 women with TS and liver enzymes; ALT, AlKP and GGT. Factors affecting liver enzymes were examined such as hormone replacement therapy (HRT), age at visit and BMI. HRT was categorised as those receiving either *oral* oestrogens (oral contraceptive, oestradiol valerate & conjugated equine) or *transdermal* oestradiol. We assessed interactions between variables and liver enzyme parameters using a multiple regression. The first column of results shows the percentage of enzyme measurements that were above the reference range. Results for partial correlation coefficients on multiple linear regression are shown in the adjacent three columns with each enzyme tested separately as the dependent variable (* represents $P<0.05$).

	Number (%) values above the reference	Age	BMI	HRT (oral vs transdermal)
ALT	1494/4420 (43.8%)	0.17*	0.20*	0.08*
AlKP	1269/4603 (27.6%)	0.02	0.14*	0.06*
GGT	1080/2163 (49.9%)	0.31*	0.27*	0.03

Conclusions
BMI was the greatest influence on all liver enzymes with age showing a positive influence on ALT and GGT. With regard to oestrogen use, oral oestrogen was associated with lower enzyme levels compared to transdermal oestradiol as a weak independent influence on ALT and AlkP. Weight loss is a priority for adult women with TS and raised liver enzyme although extent of reversibility is get to be proven.

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P953

Is it all about deiodinase after all? Effects of correction normal high tsh in women with infertility on pregnacy outcome

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Introduction
Progress in the field of infertility research and an increasing number of In Vitro Fertilizations (IVF) with intensive approach to sterility has opened new doubts about the impact of thyroid gland in the conception as well as pregnancy outcomes. Standard access to the levels of TSH and interpretation values as subclinical or clinical forms of hypothyroidism in this population has not proved to be quite correct.After the IVF guidelinesses begun to emphasize the amount of TSH of 2.5 mIU / l as the preferred upper limit for IVF, often have changes in thyrologists approach to this problem. The appearance of new organ (placenta) and intensive deiodinase activity is changing thyroid hormone metabolism.
Objective
Prove that correction of normal-high TSH values from 2.5 to 6.0 mIU /l with levothyroxine to below 2.5 mIU /l has an impact on the outcome of pregnancy. Discuss different mechanisms that might affect pregnancy outcome.
Materials and methods
Retrospectively in the last 8 years, a group of 60 patients who were at least two years in marriage and with the diagnosis of infertility, previously not given birth, were subjected to various procedures (VTO, insemination, etc.) and investigation group has not been previously treated for therapy thyroid gland diseases. From this group we excluded women with known tendency to thrombophilya and proven hyperprolactinemia. Patients had initial TSH levels (TSH1) of 2.5 to 6.0 mIU /l and normal T4 values, were treated with levothyroxine to TSH suppression below 2.5 mIU/l. Determined last TSH (TSH2) before pregnancy. During pregnancy, all patients maintained TSH levels below 2.5 mIU /l. Followed by the outcome of the pregnancy, which is regarded as: delivered, miscarriage, no pregnancy.
Results
Forty-three patients (71.6%) delivered successfully, 13 patients (21.6%) got pregnant but had a miscarriage, 4 had not got pregnant (6.66%) p(TSH1)=0,751 , p(TSH2)=0,580
Conclusion
During the follow-up of this group of respondents, obtained a high number of successfully conceived and delivered pregnancies (71.6%), the number of spontaneous miscarriages was discreetly higher than in the general population. It might happened that changes in deiodinase activity are the reason for these results or some other mechanism (TSH independent).

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P954

A case of 17 alpha-hydroxylase deficiency in a 46,XX patient: but where are Mullerian ducts?

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Introduction
The 17 α-hydroxylase deficiency is a rare form of congenital adrenal hyperplasia. It is characterized by amenorrhea, impuberism, hypertension and hypokalemia. We report a case of 17α-hydroxylase deficiency in a patient with a 46,XX karyotype, which contrasted with the absence of Mullerian duct.
Case report
An18-year-old female was referred for primary amenorrhea. Her parents were cousins. Her sister, who had the same features, died suddenly at the age of 25. Physical examination showed hypertension (160/90 mm Hg), impuberism (S1P1 stage of Tanner classification) and normal female pre-pubertal external genitalia. The karyotype was 46, XX. Biological evaluation showed hypokalemia, primary hyperaldosteronism and low levels of all steroid hormones requiring α-hydroxylation (cortisol, 17α-hydroxy progesterone, dehydroepiandrosterone sulfate, 11 desoxycortisol, Δ4 androstenedione and testosterone). Thus, the diagnosis of 17 α-hydroxylase deficiency has been suspected. However, ultrasound and pelvic MRI did not show gonads or Mullerian ducts, which did not fit with the 46, XX karyotype. The patient was treated with hydrocortisone and spironolactone, with normalization of blood pressure and kaliemia. Estrogen replacement therapy was started to induce pubertal development. The genetic study is planned.
Conclusion
In contrast to other forms of congenital adrenal hyperplasia, the diagnosis of 17 α-hydroxylase deficiency is usually delayed to adulthood. It must be suspected in all young hypertensive patients with hypokalemia and amenorrhea. We have found no previous similar case with gonadal agenesis and absent Mullerian ducts in 46,XX subjects with 17 α-hydroxylase deficiency. Further exploration may be needed to explain this association.

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P955

Breast cancer in transgender persons receiving gender affirming hormone treatment: results of a nationwide cohort study

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Background
Transpersons can receive gender affirming hormone therapy (HT) to induce physical changes. Little is known about the effect of HT on breast cancer (BC) risk.
Objectives
To study the prevalence and characteristics of BC in transpersons with HT and to compare this prevalence with the general Dutch male and female population.
Methods
Adult transpersons who were seen after 1991 and started HT in the VUmc were included. This cohort was linked in August 2017 to the nationwide PALGA database, which registers histopathology and cytopathology in the Netherlands. Information about the date of diagnosis, type of BC, and hormone receptor status was retrieved.
Results
2,567 transwomen (median age at start of HT 30 years, inter quartile range (IQR) 23-41) and 1,324 transmen (median age at start of HT 23 years, IQR 19-31) were included with a follow-up time of 22,576 and 10,109 person-years, respectively. In transwomen, 18 BC cases were identified, while 72 BC cases (based on Dutch female reference rates) and 0.4 cases (based on Dutch male reference rates) were expected. In transmen, 4 cases were identified, while 21 and 0.1 cases were expected, respectively. Three transmen were diagnosed with BC several years after mastectomy. The median age at diagnosis was 51 years (range 30-73) in transwomen and 47 years (range 35-59) in transmen, which is lower than the average 61 years in the female reference population. Median number of years of HT before BC diagnosis was 222 months (range 79-490) in transwomen and 176 months (range 23-199) in transmen. In both groups, the most prevalent type of BC was ductal carcinoma, with 67% and 75%, respectively. In transwomen, 80% of the tumors were estrogen receptor positive (ER+), 67% progesterone receptor positive (PR+) and 7% human epidermal growth factor receptor-2 positive (HER2/neu+). In transmen, 50% was ER+, 50% PR+, and 25% HER2/neu+.
Conclusions
This study showed an increased risk of BC compared with the Dutch male reference population. Although the age at diagnosis was lower, the risk of BC in transpersons is still lower than in the Dutch female reference population.

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P956

The role of lipids in prediction of gestational diabetes mellitus

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Introduction
Gestational diabetes(GDM) is a kind of diabetes that can happen during pregnancy. Many women who have GDM, get type 2 diabetes later in life. GDM is more likely for women who are overweight, women with family members who have type 2 diabetes and women who are American Indian. During pregnancy of healthy women, it is usual for blood lipids to increase significantly. Total cholesterol, HDL- and LDL-cholesterol increase 25-50%, triglycerides increase twice to four times and there is also an increase of apolipoproteins B. High triglycerides prior to pregnancy may develop severe hypertriglyceridemia (third trimester).
Aim
The aim of the study is to estimate the predictive value of lipid levels at the beginning of pregnancy to the development of gestational diabetes mellitus.
Materials and methods
The study includes 114 pregnant women, without lipid disorders before pregnancy. In study, in first trimester of pregnancy(10-11 week of gestation), we measured: fasting lipid profile(cholesterol, tryglicerides, low density proteins, high density proteins), hsCRP, total weight, total height and body mass index. All pregnant women finished OGT test in 24-28 week of gestation (performed 75-g OGTT with plasma glucose measurement before, 1h and 2h after). Patients were divided into two groups: patients with developed gestational diabetes(GDM) and patients without gestational diabetes(nonGDM). The measured parameters(in first trimester), between GDM and nonGDM group were compared. We used Student's T test.
Results
In our study 12 patients develop GDM(10.25%), 102 patients(89.75%) were with normal OGTT. Patients with developed GDM were older(28.75±2.01 vs25.22±1.78 years), with higher BMI (28.57±4.02VS26.46±1.26 kg/m2), with higher levels of triglycerides (2.26±0.87vs1.87±1.12mmol/l), higher levels of hsCRP(2.32±0.99vs1.76±0.76) and lower levels of HDL (1.20±0.16 vs1.41±0.32 mmol/l) ($P<0.05$). The levels of cholesterole (4.24±1.24v4.27±0.85mmol/l) and LDLc (2.87±0.56 vs2.91±0.71 mmol/l) were similar ($p>0.05$). Seven(58.33%) of GDM patients have DM in family. Fifteen(14.7%) of nonGTT patients have DM in family.
Conclusion
Pregnant women who have higher values of triglycerides and lower HDL values, in first trimester of pregnancy, are more likely to develop GDM. Also, older pregnant women, those with higher BMI(in the first trimester) and those with DM history in family are at a greater risk of GDM.

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P957

Biological exploration of hirsutism: Tunisian experience

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Introduction
In women, androgens are produced by adrenal glands and ovaries. In peripheral tissues, they result from a conversion of present androgens in the blood circulation. Androgens measurement are of interest in the exploration of hirsutism.

Materiel and methods
Retrospective study was conducted over 12 months from January, 2016 to December 2017 in Biochemistry Laboratory of Habib Bourguiba Hospital. Testosterone and prolactin assay were performed using electrochemuluminescence technique (cobas 6000, Roche). S DHEA, delta 4 androstenedione (Δ4 A) and 17 OH progesterone (17 OHP) were performed using ELISA technique. Statistical analysis were performed using Epi Info 7.
Results
Fifty-four women with suspicion of hirsutism were included in the study. The average age of patients was 33 ± 14 ans. Prescriptions came mainly from Endocrinology (57.3%), dermatology(9.48%) , gynecology(8.2%), pediatrics(8.2%) departments. Mean value of Testosterone and prolactin were 0.49 ± 0.56 ng/ml and 21.85 ± 10.61 ng/ml respectively. 17 OHP level was 2.79 ± 4.42 ng/ml while s DHEA and Δ4 A were 1.81 ± 1 µg /ml (RR: 0.4- 2.17 ng/ml) and 3.44 ± 3.44 ng/ml (RR: 0.75 – 3.89 ng/ml) respectively. Testosterone values were upper than 0.6 ng/ml in only 2 cases while 17 OH progesterone values were upper than reference range in 80%.
Conclusion
17 OH P seems to be more sensitive in the diagnosis of hirsutism than testosterone but the biological interpretation of hormonal assays cannot be done without detailed patients' clinical information

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P958

A new balanced autosomal translocation as a cause of premature ovarian insufficiency

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Premature Ovarian Insufficiency (POI) is defined as impairement of ovarian function in women under 40 years, with a incidence between 1-4% in women of reproductive age. Among the major identified causes of Premature Ovarian Insufficiency, genetic factors related with X-chromosome are widely described. However, autosome defects are less common found and are related generally with genetic mutations instead of structural abnormalities of them. Thefor, we report a relevant case of POI with balanced translocation between chromosomes 9 and 10. Our patient had puberal development and her first menstrual period at the age of 12, both spontaneously. After 2 years of regular cycles, she stopped menstruation. Laboratory investigations showed FSH and LH within menopausal range, with estradiol <50 pg/ml. Ultrasonography demostrated small uterus and left ovary, right ovary was not seen. Genetic testing showed karyotype 46,XX,t(9;10)(p24;q23). It should be noted that 9p24.3 region codes for DMRT1 an DMRT2 genes, which encode for transcription factors involved in indifferent gonad formation. Finally, this autosomal translocation is not yet described as a cause of POI.

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Male Reproduction

P959

Infertility caused by Chapelle syndrome

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Introduction
Testicular disorder of sexual development (XX male syndrome; Chapelle syndrome) is a rare clinical condition. Incidence is 1:20 000 in newborn males. Characteristics of syndrome include hypogonadism, gynecomastia, and infertility resulting from the azoospermia. Diagnosis is mainly established after puberty. Clinical manifestations could be heterogeneous, but external genitalia appear to be completely virilized in 90% of 46,XX males: SRY-positive. Other manifestations such as hypospadias, undescended testes, or various degrees of inadequate virilization in the external genitalia are seen in 10% of the cases: SRY-negative.
Case report
In this paper we described a 31-year-old male with complete masculinization referred to geneticist because of a history of several years of infertility and established azoospermia. He had hypergonadotropic hypogonadism. FSH was elevated, LH was elevated, testosteron was lower. Peripheral blood karyotype showed a normal female karyotype (46,XX). FISH analysis revealed that SRY locus had been translocated to the short (p) arm of the X chromosome. A testosterone replacement therapy was initiated.
Conclusion
Etiology of infertility is heterogeneous. Karyotype should be performed in all males with azoospermia or severe oligospermia. Also, there is necessity of multidisciplinary approach.

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P960

Endogenous testosterone supports spermatogenesis even in the absence of gonadotrophins: evidence from a case report

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Background
In patients with testicular dysgenesis syndrome, reduced semen quality and testicular cancer are common. We report a case of a testicular tumour in a patient with a history of cryptorchidism and oligoasthenospermia. He had an unusual hormonal profile, which was not fully explained by the pathological findings.
Case
A 31-year-old man was referred to our tertiary care andrology unit for primary infertility with a history of bilateral orchidopexy during childhood. Testes were small (12 cc). Gynaecomastia was absent. Semen analysis repeatedly showed oligoasthenospermia (2.4 to 7.1 million/mL, 85 to 92% immotile). Gonadotropins (LH and FSH <0.1 U/L) were undetectable, but testosterone and estradiol were normal (850.7 ng/dL and 38.6 ng/L). Prolactin, other pituitary hormones, DHEAS, AFP, HCG and inhibin B were also normal. He denied using anabolic steroids. Suppressed gonadotrophins suggested a sex steroid producing testicular tumour. However, scrotal ultrasound only showed diffuse microcalcifications and three millimetric hypolucent lesions in the left testis, but no intratesticular mass. There were no suspicious lesions nor microcalcifications in the right testis. To further investigate the possibility of increased testicular sex steroid production, selective testicular venous sampling was performed. In the left spermatic vein, testosterone and estradiol levels were very high (3744 ng/dL and 378 ng/L), with a testis-to-periphery gradient of 4.4 and 9.0 respectively. There was no gradient in the right spermatic vein. These results confirmed increased sex steroid producing in the left testis. However, histopathological examination after orchidectomy revealed a multifocal seminoma (largest diameter 3 mm) and profuse germ cell neoplasia in situ. There were neither isolated syncytiotrophoblastic cells, nor choriocarcinoma. Leydig cell hyperplasia was present without Leydig cell tumour. HCG was remeasured with three different methods, all showing very low HCG between 0.6 and 1.1 IU/L. After orchidectomy gonadotrophin levels increased (LH 24.3 U/L, FSH 10.3 U/L), with normal total testosterone and estradiol, indicating recovery of suppression of the hypothalamic-pituitary-testis axis. Sperm concentration increased (10 million/mL.)
Key messages
Our case shows that endogenous testosterone may support spermatogenesis even without gonadotropins.
In patients with suppressed gonadotropins, normal sex steroid levels and no testicular mass, selective testicular venous sampling can be useful in identifying the site of hormonal overproduction.
Thus far, the pathology findings cannot explain the hormonal profile. Further investigations are therefore ongoing.

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P961

Differential effects of genetically inherited – and high fat diet induced – obesity on spermatogenesis in adult male rats

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Obesity, a new world syndrome, is defined as excessive white adipose tissue accumulation, that may impair health leading to severe metabolic and reproductive complications affecting millions of people of different age groups. Recent studies have shown that incidence of male obesity induced fertility issues are rising in couples undergoing assisted reproductive technologies suggesting that obesity is emerging as an established risk factor for male infertility or subfertility. Obesity is a multifactorial condition with predominantly genetic and/or environmental causes. No studies have compared genetically inherited and high fat diet induced obesity effects on spermatogenesis. Thus, our present study aims to delineate effects of obesity on spermatogenesis using two male rat models: genetically inherited obese (GIO) – WNIN/Ob and diet induced obese (DIO) – High fat diet. Terminal body weights were similar in both groups, but, differential effects on adiposity index were observed in both the groups. We observed a significant decrease in caudal sperm counts in GIO group but not in DIO group despite body weights being similar in both the groups. To study the specific cause of reduced sperm counts in GIO group, not in DIO group, flow cytometry and germ cell specific marker expression studies in testis revealed that both genetically inherited and diet induced obesity affects mitosis process by increasing spermatogonial proliferation. In GIO group, both meiosis and differentiation process was affected by decreasing spermatocyte population and increasing round spermatid population as well as decrease in elongated spermatid population confirming the decrease in caudal sperm counts whereas in DIO group, it was unaffected. Further, gene expression studies in testis in GIO and DIO group revealed differential expression of genes involved in various aspects of spermatogenesis mainly primary spermatocyte progression and spermiogenesis process, reproductive hormone receptors, leptin signaling molecular players, pro-inflammatory cytokines and cell cycle mediators. Taken together, our study shows that the differences in the effects of genetically inherited and diet induced obesity on spermatogenesis is based on the difference in adiposity index and not due to high terminal body weights. This suggests that the discrepancies in the literature concerning human obesity induced fertility issues could be due to combination of both genetic and environmental factors as well as due to the difference in the amount and distribution of white adipose tissue which could be leading to infertility in some obese individuals but not in all.

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Male Reproduction

P962

Hematological indices in congenital hypogonadism and the effect of testosterone replacement therapy: A retrospective study

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Introduction
Patients with hypogonadism are at increased risk for cardiovascular diseases. Mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) are hematological indices that are surrogate markers of adverse cardiovascular outcomes. This study investigated the platelet count, MPV levels, PLR, and NLR in patients with congenital hypogonadotrophic hypogonadism (CHH) and also studied the effect of testosterone replacement therapy (TRT) on these parameters.
Methods
A total of 67 young male patients with CHH (mean age: 21.5 ± 2.0 years) and 68 healthy control subjects (mean age: 21.9 ± 1.3 years) were enrolled in the study. The demographic parameters, homeostatic model assessment-insulin resistance (HOMA-IR), platelet count, MPV, PLR, and NLR were measured in patients with CHH and healthy controls before and after TRT.
Results
The patients had higher WC ($P=0.04$), triglycerides ($P=0.02$), insulin ($P<0.001$), HOMA-IR ($P<0.001$), platelet count ($P=0.001$), MPV ($P=0.004$), and PLR ($P=0.003$) levels and lower FSH, LH, and total testosterone ($P<0.001$ for all) levels than the healthy controls. After 5.85 ± 2.13 months of TRT, the patients had significantly elevated BMI, WC, total testosterone, and HOMA-IR ($P<0.001$, $P=0.001$, $P<0.001$, and $P=0.03$, respectively) and decreased HDL-C levels ($P<0.001$); however, the alterations in platelet count, MPV levels, PLR, and NLR were not significant. There was also a significant correlation between total testosterone level and platelet count ($r=-0.23$, $P=0.009$), MPV ($r=-0.0.22$, $P=0.013$), and PLR. ($r=-0.0.22$, $P=0.014$).
Conclusion
The present study showed that platelet activation may play a pivotal role in the pathogenesis of cardiometabolic risk of patients with hypogonadism. Moreover, the short time TRT in treatment naïve young patients with CHH did not have any effect on the platelet count and size.

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P963

Hypogonadism and mortality in type 2 diabetic men

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Introduction
Low testosterone serum levels are associated with increased mortality in non-diabetic males. However, knowledge about the association between male hypogonadism and mortality among type 2 diabetic (T2DM) men is limited due to short follow-up periods in the few existing studies.
Objective
To assess the association between hypogonadism and mortality in diabetic men.
Material and methods
263 unselected men with T2DM (mean age 63.9 ± 10.5 years) were followed prospectively until death or December 1, 2017, during a period of 8 ± 3.9 years. Diagnosis of hypogonadism was established adding low total testosterone (TT) serum levels and hypogonadal symptoms (positive ADAM questionnaire). Three different thresholds for low testosterone were used (TT <3.4, <3 and <2.3 ng/ml). The survival in hypogonadal vs eugonadal men was analyzed with Kaplan-Meier survival curves (univariate analysis) and Cox regression (multivariate analysis).
Results
A total of 56 patients (21.3%) died during follow-up. Lower levels of TT (3.9 vs 4.4 ng/ml, $P=0.044$), free testosterone (7 vs 8.9 ng/dl; $P=0.011$) and bioavailable testosterone (164.2 vs 218.9 ng/dl; $P=0.003$) were found in deceased diabetic patients than in the group of survivors. The percentage of patients who died was higher in the hypogonadal group than in eugonadal diabetic men for all three thresholds (TT <3.4 ng/ml: 31.4 vs 17.7%, $P=0.026$, OR = 2.1 (95% CI = 1.1–4); TT <3 ng/ml: 33.3 vs 18.8%, $P=0.044$, OR = 2.2 (95% CI = 1.1–4.4); TT <2.3 ng/ml: 46.7% vs 18%, $P=0.001$, OR = 4 (95% CI = 1.8–8.8)). Survival was significantly lower in hypogonadal than in eugonadal men, and that was also demonstrated by using the three thresholds: TT <3.4 ng/ml: 68.6% vs 82.7% (Log-rank 8.5, $P=0.004$); TT <3 ng/ml: 66.7% vs 81.6% (Log-rank 7.7, $P=0.005$) and TT <2.3 ng/ml: 53.3% vs 82.3% (Log-rank 21.4, $P<0.001$). In addition, the mean time of survival was lower in hypogonadal than in eugonadal men (TT <3.4 ng/ml: 11.3 vs 14.3 years, $P=0.004$; TT <3 ng/ml: 11 vs 14.1 years, $P=0.005$ and TT <2.3 ng/ml: 7.7 vs 14.2 years, $P<0.001$). In the multivariate analysis, hypogonadism increased the risk of mortality (HR = 2.3, 95% CI = 1.2–4.3, $P=0.01$) independently of age, poor glycemic control, renal failure and the presence of macrovascular disease.
Conclusions
In the longest follow-up study reported so far we show that hypogonadism is associated with decreased survival in diabetic men. Mortality rates and mean time of survival were associated with the severity of male hypogonadism.

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P964

Impact of testosterone administration to female-to-male transsexuals on cardiovascular risk factors

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Introduction
Cross sex hormonal therapy with testosterone is used in female-to-male transgender people to induce the desired secondary sexual features; this could lead to an increased risk of cardiovascular diseases. Data published on this subject is scarce and contradictory.
Objective
To evaluate effects on weight, inflammatory and prothrombotic parameters, lipid profile, and insulin resistance after 3–4 months of testosterone treatment in transsexual men.
Materials and methods
Prospective study including 25 transsexual men who started treatment with testosterone between 2016 and 2017. Average was 23 ± 9.6 years of age. Those with known dyslipidemia, diabetes or thrombophilia were excluded. All of them started the treatment with 250 mg of i.m. testosterone cypionate every 21 days, except for 5 patients who started with 50 mg a day of transdermal testosterone gel, remaining in amenorrhea. Dietary and increased physical activity measures were promoted in all cases.
Results
There was a mean increase in weight after 3–4 months of treatment (72.4 ± 23.4 vs 74.4 ± 24.6 kg, $P = 0.026$), although it was very individually variable. 56% of the participants gained weight (3.7 ± 3.3 kg), while the rest (44%) remained stable or lost weight (−1.5 ± 1 kg). Testosterone treatment was associated with an increase in LDL levels, from 99.4 ± 32 to 105.4 ± 32 mg/dl ($P = 0.017$) and TG levels, from 69.6 ± 28.5 to 86.0 ± 38.2 mg/dl ($P = 0.048$). HDL levels did also decrease (54.9 ± 14.1 vs 44.8 ± 10.6 mg/dl, $P < 0.001$), as those of Apolipoprotein A (161.5 ± 24.4 vs 141.7 ± 23.7 mg/dl, $P = 0.005$). No differences were observed both in CRPus and fibrinogen levels. Homocysteine levels did increase (8.6 ± 2.5 vs 12.1 ± 7.9 umol/l, $P = 0.037$). Fasting glucose level dropped from 87.6 ± 9.6 to 83.6 ± 10.0 mg/dl ($P = 0.01$), but no differences were found in glycosylated hemoglobin levels nor in the HOMA index. An increase in total hemoglobin (13.2 ± 1.0 vs 14.7 ± 1.4 mg/dl, $P < 0.001$) and hematocrit (40.7 ± 3.0 vs 44.9 ± 4.0%, $P < 0.001$) levels was observed, not reaching pathological values in any case. No differences were observed in the platelet count. No positive correlation was observed between higher testosterone or estradiol levels and the variables studied.
Conclusions
There is a worsening of analytical parameters related to cardiovascular risk. There is a weight gain that could be controlled by promoting dietary and physical activity measures.

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P965

Triglyceride-Glucose index levels in patients with congenital hypogonadism

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Introduction
It is well known that patients with hypogonadism are at increased risk for insulin resistance and cardiovascular diseases. In many studies homeostatic model assessment-insulin resistance (HOMA-IR) formulation is used for the evaluation of insulin resistance. Recently, a simple and inexpensive approach to evaluate for insulin resistance has been developed, the Triglyceride – Glucose (TyG) index. This particular index is based on measuring the levels of fasting triglycerides and glucose. This study investigated the TyG index as a useful surrogate marker of insulin resistance among patients with congenital hypo gonadotrophic hypogonadism (CHH).
Methods
A total of 154 young male patients with CHH (mean age: 21.54 ± 1.95 years) and 115 healthy control subjects (mean age: 22.81 ± 1.45 years) were enrolled in the study. The demographic and laboratory parameters, plasma ADMA, hsCRP, HOMA-IR levels and TyG index were measured in healthy controls and patients with CHH, before and after TRT.
Results
The patients had higher waist circumference (WC, $P = 0.011$), systolic blood pressure (SBP, $P = 0.011$), triglycerides (Tg, $P < 0.001$), insulin ($P < 0.001$), asymmetric dimethylarginine (ADMA, $P < 0.001$), HOMA-IR ($P < 0.001$) and TyG index ($P = 0.004$) levels and lower follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone ($P < 0.001$ for all) levels than the healthy controls. After 5.85 ± 2.13 months of TRT, the patients had significantly elevated BMI ($P < 0.001$), WC ($P < 0.001$), SBP ($P = 0.002$), Tg ($P < 0.001$), total testosterone ($P = 0.012$), HOMA-IR ($P < 0.001$), ADMA ($P < 0.001$) and TyG index ($P < 0.001$) and decreased HDL-C levels ($P < 0.001$). There was also a significant correlation between TyG index and BMI ($r = 0.15$, $P = 0.03$), WC ($r = 0.25$, $P < 0.001$), HDL-C ($r = -0.21$, $P = 0.001$), LDL-C ($r = 0.15$, $P = 0.032$) and ADMA ($r = 0.17$, $P = 0.03$) levels.
Conclusion
The results of the present study show that patients with CHH have elevated TyG index which is an easily calculated and inexpensive parameter that can indicate insulin resistance. TyG index is further increased after TRT and also related to surrogate marker of endothelial dysfunction. Prospective follow-up studies are warranted to clarify the role of TyG index in predicting cardiometabolic risk in patients with hypogonadism.

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P966

Effects of cross-sex hormone treatment on body composition in transgender persons

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Background
Cross-sex hormone treatments are used to masculinize or feminize the bodies of female-to-male (FtM) or male-to-female (MtF) transsexuals, respectively. Redistribution of fat mass is expected to occur during the first 1–6 months in transgender males and in the first 3–12 months in transgender females.
Objective
To examine the effects of cross-gender sex hormone therapy (CHT) on body composition in transsexual men and women.
Materials and methods
Observational study. 40 transsexual men and women assisted in the Gender Identity Unit of an endocrinology community from January to September 2017. We measured weight, body mass index(BMI) and body composition by bioelectrical impedance analysis(BIA) at baseline and after mean duration of CHT of 2 years.
Results
We evaluated 40 transsexuals, 19 male-to-female (MtF: 47.5%) and 21 female to male (FtM: 52.5%). Mean age 23.86 ± 11.25 years, mean duration of CHT of 24.7 ± 39.9 months. In MtF(68.8% oral estradiol, 31.2% estradiol transdermal patch,83.3% cyproterone acetate), weight(Kg) and BMI(Kg/m2) increased from 72.12 ± 19.04 to 73.17 ± 19.96 ($P < 0.03$) and from 23.8 ± 5.79 to 24.03 ± 5.85($P = 0.04$) respectively; difference in body composition by BIA were also observed: fat mass(Kg) from 9.79 ± 7.62 to 12.3 ± 0.43($P = 0.03$), muscle mass(Kg) 55.45 ± 9.24 to 56.05 ± 8.76 ($P = 0.015$), body water 40.60 ± 6.75 to 41.02 ± 6.42 ($P = 0.04$). FtM (76.9% testosterone cypionate,23.1% testosterone undecanoate) also presented significant difference in body composition:fat mass(Kg) from 18.50 ± 3.55 to 14.14 ± 3.95($P = 0.04$), muscle mass(Kg)

46.44 ± 2.27 to 49.70 ± 6.55($P = 0.026$), body water 36.55 ± 5.57 to 33.77 ± 1.84 ($P = 0.042$). No significant difference in weight and BMI were observed.
Conclusion
Oral estradiol is the most frequent estrogen preparation used in transgender woman and testosterone cypionate in transgender men. Testosterone treatment in transgender males resulted in increased muscle mass and decreased fat mass. In transgender females, CHT is associated with change in fat mass redistribution although no difference in weight and BMI were observed.

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P967

Erectile Dysfunction – The hidden sickness we don't seek

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Introduction
Erectile dysfunction (ED) is highly prevalent and negatively impacts the patient's and the partner's quality of life. It is a well-established red flag for ongoing neuro-vascular disease and a predictor of coronary, cerebral and peripheral arterial disease (PAD). Our aim was to document how often do clinicians investigate ED and use it as a predictor of neuro-vascular pathology to trigger a thorough revision of cardiovascular risk factors (CVRF). This assessment was indirectly performed, using an original questionnaire (Qr) aiming to identify the patient's/clinician's awareness of ED. The Qr ascertained self-considered ED; ED approach at any hospital visit; ED presence and degree by the IIEF-5 questionnaire and investigated hypogonadism, comorbidities and life-style. The participants filled the Qr voluntarily, autonomously and anonymously.
Results
Participants ($n = 52$) with mean age 52.5 (32–72) y.o., 65% within 40–70 y.o. range, self-reported ED in 40.6% cases. Of these, 6% said to have been questioned by their doctors about ED. The remaining 84%, though they answered they would have liked to have discussed ED in a visit, only 9% had ever had that initiative. Among all patients, only 9.6% had been interrogated by their physicians about ED. Of the patients self-reporting ED using drugs (11.5%), 5.7% did so with over the counter. Hypogonadism symptoms/signs were reported by 23% (50% self-considered to have ED) and only 6% had ever been questioned about related symptoms. Patients reporting 2 or more hypogonadism specific symptoms ($n = 3$), had moderate ED on the IIEF-5 questionnaire. IIEF-5 assessment revealed an ED prevalence of 60%. In 44% it was moderate-severe, 89% of these patients had self-reported ED but only 1 had been ever questioned about it and only 2 had ever had the initiative to mention it. Obesity, hypertension, dyslipidaemia, inactivity, smoking, alcohol consumption, stroke, AMI and PAD were more prevalent in the group with ED (IIEF-5), but not in the group who considered to suffer from ED.
Conclusions
The prevalence of ED was significant. Most clinicians didn't actively seek ED and most patients didn't inform their doctors about their problem. Self-reported ED validated by the IIEF-5 questionnaire was useful in the identification of patients with CVRF and established cardiovascular disease. The identification and treatment of ED impact positively not only quality of life but also cardiovascular mortality: an underestimated chance for intervention that shouldn't be missed.

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P968

Subfertility in male hypogonadotropic hypogonadism secondary to obesity: successful conception with novel use of aromatase inhibitor

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Background
Hypogonadotropic hypogonadism due to obesity in males can be challenging to treat, particularly when fertility is desired. Although weight loss is ideal, this is difficult to achieve quickly, while testosterone replacement further suppresses spermatogenesis. Aromatase inhibitors have been suggested to improve spermatogenesis in idiopathic male hypogonadism, but there are no large scale studies to support this. Aromatase inhibitors may be even more efficacious in obesity-related hypogonadism due to increased aromatase activity causing high estrogen levels and suppressed gonadotrophins. We describe a case of successful conception after letrozole was initiated.
Clinical Case
A 30-year-old gentleman with morbid obesity (BMI 43.7 kg/m^2) presented with subfertility. Secondary causes of obesity were excluded. Preliminary workup showed hypogonadotropic hypogonadism (repeated low 8-am testosterone, 3.70 nmol/L, calculated testosterone 148 pmol/L) with inappropriately normal FSH and LH levels (FSH 2.85 IU/l, LH 3.93 IU/l). The other pituitary hormones were normal and pituitary imaging did not show any lesion. Initial semen analysis done showed oligo-astheno-teratozoospermia (Density 4 mil/mL, Motility 10%), suggestive of impaired spermatogenesis. The patient was counselled on lifestyle changes to achieve weight loss. He declined pharmacological therapy for his obesity, as well as bariatric surgery. However, the patient was not able to achieve significant weight loss and the couple was keen to conceive soon. Letrozole, an aromatase inhibitor, was started at 1.25 mg once a week. After 7 weeks of treatment, there was a rise in FSH (from 2.53 IU/l to 7.11 IU/l) and LH (from 3.58 to 10.5 IU/l), and corresponding rise in 8 a.m. testosterone levels from 3.31 nmol/L to 14.04 nmol/L, without a significant change in weight. He noted increase in his libido and frequency of morning erections. Within another four months, the couple successfully conceived, notably during his wife's first cycle of assisted reproduction (IVF). Letrozole was discontinued soon after, with resumption of lifestyle measures to encourage weight loss.
Conclusion
Although aromatase inhibitors have been used sporadically to improve male hypogonadism, this unique case shows successful conception after a short course of letrozole, achieving rapid improvement in hypogonadism. Although they may not correct other important issues, such as metabolic complications in obesity, a course of aromatase inhibitors may be a useful adjunct to other measures like weight loss, in improving subfertility in obesity-related hypogonadotrophic hypogonadism.

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P969

Leptin targets in the male reproductive tract of mice

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Leptin is best known as an appetite and metabolic rate modulator secreted from fat, but it also has a range of other functions including modulation in reproductive physiology. To date, most studies examining the role of leptin in male reproduction have focussed on individual tissues, often *in vitro*. In the current report, a bolus physiological dose of iodinated leptin was administered intravenously to male mice to and samples collected over a one hour time course to determine potential targets for leptin action in the male reproductive tract. The testis and the epididymis accumulated approximately 0.3% of the administered dose, remaining relatively stable over the time course. In the seminal vesicles, the dose recovered increased from 0.35 ± 0.1% to 1.37 ± 0.3% of the dose from 5 to 45 min after administration. In terms of dose recovered per gram of tissue, recovery from testis and epididymis remained relatively stable at approximately 0.9% dose/g, 2.5% dose/g, respectively. Recovery from the seminal vesicles 5 min after administration was 1.14 ± 0.1%dose/g, increasing to 4.15 ± 0.4%dose/g 45 min after administration, before a decline to 3.10 ± 0.2% dose/g observed 60 min post-injection. Major targets for leptin binding have been characterised in previous studies including work from out lab. These studies showed that leptin was rapidly cleared from these tissues. In the male reproductive tract leptin appears to accumulate, with the seminal vesicles being a preferential target, although the testis and epididymis also accumulate leptin for a period of time. Leptin receptors are expressed in each of these tissues, and leptin signalling has been shown to attenuate testosterone secretion in the testis, while in the epididymis leptin increases spermatozoa differentiation. However, it is still

unclear why leptin would accumulate in the seminal vesicles. Leptin and the soluble leptin receptor (LepRe) have been recovered from ejaculate and, leptin is known to facilitate *in vitro* fertilisation and implantation, and LepRe increases the half-life of leptin. Thus, leptin in the male reproductive tract may play a role in the normal fertilisation and implantation processes.

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P970

A case of Wolfram syndrome with primary gonadal insufficiency

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Introduction
Wolfram syndrome is characterized by diabetes mellitus (DM), diabetes insipidus (DI), optic atrophy and sensorineural deafness. DM is the first manifestation and optic atrophy also onsets in the first decade of life. The onsets of DI and sensorineural deafness are in the second decade, urinary tract abnormalities are in the third decade and neurologic abnormalities are in the fourth decade respectively. Hypogonadotrophic hypogonadism is a usual manifestation of the syndrome, however, as in our case, hypergonadotrophic hypogonadism can be rarely seen.
Case report
A 24- year old male patient admitted to our clinic with the complaints of mouth dryness, polyuria and polydipsia. The onset of polyuria, polydipsia, and blurred vision was at the age of six. He was diagnosed with tip 1 DM at the age of seven and intensive insulin therapy was instituted subsequently. It was noticed that despite the good glycemic control, the daily liquid intake of the patient was 10 liter, and the urine output was 9.5 l. The visual complaints of the patient were thought to be related to myopia and diabetic retinopathy. Our patient had complaints of loss of libido, impotence, erectile and ejaculatory dysfunction for the last 6 months. The insulin therapy was started as insulin aspart 4 unit tid and insulin detemir 12 unit per day. In the physical examination; bilateral grade 3 gynecomastia was observed. In the hormonal panel; FSH: 45 U/l (N:1.5–12.7), LH:28.4 U/l (N:1.7–8.6), total testosterone: 3.83 ng/ml (N:3–10 ng/ml), free testosterone: 2.15 pg/ml (N:12,00–30,00 pg/ml). In the bone mineral densitometry, the Z scores were -2.3 S.D. and revealed low bone mass for chronologic age. Spermiogram was reported as azoospermia. In the cytogenetic studies male karyotype 46, XY was confirmed. The fluid deprivation test was done and according to the test results the patient was diagnosed with diabetes insipidus. In the fundus examination bilateral optic atrophy was diagnosed. In the audiogram, the hearing loss with high-frequency sounds which considered to be related to sensorineural deafness was observed. As the primary treatment of primary hypogonadism, testosterone was started. Because of the minimal regression of bilateral gynecomastia with testosterone therapy, the patient was consulted with plastic and reconstructive surgery.
Conclusion
As in our case, the patients diagnosed with Wolfram syndrome requires long-term follow-up. Early diagnosis and appropriate hormone replacement improve the quality of patients life.

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P971

Child wish and fertility preservation in assigned male at birth transgender persons living in Belgium

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Objectives
Transgender persons undergoing gender affirming hormonal and/or surgical care, are at risk of reduced fertility. Although theoretically, the options for assigned male at birth (AMAB) transgender people to fulfill their child wish are extensive, research in transgender women shows low fertility preservation utilization. Ideas and concerns of AMAB transgender persons regarding fertility preservation and child wish have never been reported in a large, non-clinical sample.
Materials and methods
A web-based survey on fertility and parenthood was conducted in Belgium in 2017, which invited persons aged ≥ 16 years who identified themselves as trans* to participate. AMAB transgender people were selected for this substudy, including transgender women (TW), transvestites and gender non binary (GNB) persons.
Results
The questionnaire was filled out by 426 participants; 254 (59.6%) AMAB (196; 77.2% transgender women (TW), 14; 5.5% transvestites and 44; 17.3% GNB persons). Fifty-five (21.6%) respondents had a current/future child wish, child wish was fulfilled in 81 (31.9%) and inexistent in 57 persons (22.4%) (other: 19.2%). Although TW were older than GNB ($P=0.14$), TW were more likely to have a child wish ($P=0.004$). In total, 196 AMAB persons (77.2%; TW: 167; 85.2% and GNB: 23; 52.3%) previously sought medical help for their gender identity, of which 30 (15.3%) considered the loss of fertility due to the transitioning process undesirable. The majority (75; 68.2% – 86 missing) did not wish for fertility preservation. Of the total AMAB population, 14 people (9.8% – 112 missing, TW: 12; 10.3%, GNB: 2; 7.7%) had frozen germ cells. The top three reasons not to proceed with fertility preservation included not feeling the need (70; 68.0%), not desiring a genetic link with (future) child(ren) (20; 19.4%) and having to postpone hormone treatment (15; 14.6%). Barriers encountered for fulfilling child wish included assumed difficulties in the adoption procedure (40; 16.1%) and fear of discrimination against the child (38; 15.3)
Conclusion
Child wish and fertility preservation utilization were lower in our AMAB population than in previous research on clinical samples. These low utilization rates reflect barriers transgender persons face when considering fertility options, including postponing hormone therapy. In the present study, TW more frequently visited a health care professional and were more likely to have a child wish, compared to GNB persons. Subsequently, TW were more likely to have germ cells frozen/consider doing so in the future, compared to GNB persons, but the use of fertility preservation remained low.

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The relationship between PTEN mutations and resistance to androgen-deprivation therapy in prostate cancer

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Background
Prostate cancer is the second leading cause of cancer-related deaths in men worldwide. A marker of poor survival in prostate cancer patients is the loss of the tumor suppressor gene *PTEN (*phosphoinositide-3-phosphatase). Deletion of PTEN occurs in approximately 40% of prostate cancer patients, and is associated with early biochemical recurrence, metastatic potential, and androgen-independence. Androgen-deprivation-therapy (ADT) remains the principal treatment of prostate cancer, despite the eventual resistance to treatment in most patients. The exact mechanism of such ADT resistance is yet to be confirmed. Thus, our study aimed to determine whether PTEN mutations play a role in ADT resistance in prostate cancer.
Methods
A case–control study was performed. Cases ($n=64$) were patients with confirmed diagnosis of prostate cancer treated with ADT, while controls ($n=58$) were subjects with benign prostatic hyperplasia. Prostate specimens were collected by needle core biopsy, or during transurethral resection of the prostate or radical prostatectomy. PTEN expression status was assessed by immunohistochemistry, and scores of 0 (no expression) and 1 (expression) were assigned to prostate tissues.

Results
Loss of PTEN expression (score 0) was 30 times more likely to occur in prostate cancer cases compared to controls. However, the presence of PTEN mutation was not significantly correlated with the pathological Gleason grade of prostate cancer severity. Mean time to ADT resistance in prostate cancer patients was 25.3 months, which was not significantly different between those with PTEN mutation (mean = 26.8 months) and those without mutation (mean = 23.5 months). However, there was a statistically significant difference in mean time to ADT resistance between those receiving the combined therapy (mean = 33.2 months) and those receiving either goserline alone (mean = 9 months) or triptoline alone (mean = 8.9 months).
Conclusion
Our results indicate that loss of PTEN expression is not sufficient to explain ADT resistance in prostate cancer patients. Combined hormonal therapy might be a promising strategy to slow the process of ADT resistance in these patients. However, further studies in larger prospective cohorts are warranted.

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P973

Male hypogonadism due to 46, XX Testicular disorder of sex development

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Introduction
46,XX testicular disorder of sex development (DSD) is a rare syndrome, which is characterized by a female karyotype in discordance with a male phenotype. It is presented with primary hypogonadism, gynecomastia and infertility. About 80–90% of 46,XX testicular DSD cases are positive for SRY gene. Appearance of external genitalia and masculinization are usually normal in 46,XX SRY-positive cases
Clinical case
A 41-year-old male came with his partner to the outpatient clinic because of low levels of testosterone detected in routine blood test. He complained about fatigue, low libido and some difficulties to maintain erections since one year. He had no history of mumps, trauma or surgery.He was 169 cm tall and he weighted 74 kg, BMI of 25.9 kg/m^2. The physical examination reveled a normal penis size, with small soft testis (2 ml). No gynecomastia was detected. Facial, body, and pubic hair were of normal density and distribution. He related his small size of testis since puberty. He had not consulted before for this Laboratoy test showed a low level of total and free testosterone, high levels of gonadotropins, normal levels of prolactin and estrogens. A karyotype and semen analysis were assessed. The karyotype analysis showed a 46,XX formula. The polymerase chain reaction analysis confirmed the presence of SRY gen. The semen analysis showed azoospermia. These results were consistent with 46, XX DSD. The diagnostic had a high emotional impact and he needed psychological support to accepted it and the fact that he was infertile He started testosterone replacement but he refused to do other tests: magnetic resonance imaging of the pelvis or bone densitometry.
Conclusion
It is important to diagnose as soon as possible this testicular DSD syndrome, to avoid its negative emotional impact and the consequences of a chronic testosterone deficiency.

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P974

DicentricisochromosomeYp in adolescent with azoospermia

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Background
Azoospermia is present at approximately 1% of the man. karyotype can show number and structure abnormalities of the sexe chromosomes.
Case
16 years old boy,who was refered to the departement of endocrinology for a failure to growth since 8 years old. This patient was resulting from a marriage between blood relations. He had a congenital bilateral hip luxation diagnosed since birth but untreated.He had a gait disorder with a low weight 32 kg <3 erd percentile and a short stature 134 cm < -3 S.D., the physicalexamination of the external genital was without anomalies. He did not have a particular endocrinal clinical disorders. The skeletal age determination was without evidence of disease.The hormonal profile was normal except these rum concentartion of follicule-stimulating hormone wich increased from 22 mUI/ml to 32 mUI/ml.The testis ultrasonography showed bilateral testis hypotrophy. A semen analysis was then required. It showed a depletion of sperm production 1.3 ml and azoospermia. The cytogenetic analysis carried out on peripheral lymphocyts with G banding revealed a 46,X, idic(Yp)(q11q22) karyotype. The rearrenged Y chromosome was accompagnied by a total duplication of the short arm Yp and a partial deletion of the long armYq.
Conclusion
This is the first report document in isochromosome Y with disruption in the SHOX, AZFb, AZFc gene area.The study is in hand to show if AZF region deletion is complete or partial.

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P975

Prolactin concentration in male-to-female transsexual subjects following cross-sex hormone therapy

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Background
Male-to-female transsexual persons use estrogens + antiandrogens to adapt their physical bodies to the female sex.Estrogens are powerful stimulators of synthesis and release of prolactin and serum prolactin levels are usually somewhat increased following estrogen treatment.
Objective
To determine prolactin levels and to assess the risk of development of prolactinoma in male-to-female transgender subjects following cross-sex hormone therapy (CHT).
Materials and methods
Retrospective longitudinal study including all male-to-female transsexual persons assisted in the Gender Identity Unit from 2015 to 2017.Clinical and laboratory data were collected before and after a mean duration of CHT of 24 months.Radiologic examinations of the pituitary were performed in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels.Transgender individuals who receive psychotropic medications were excluded.
Results
Thirty-nine male-to-female transsexual persons were included (mean age 29.05 $\pm$ 11.63 years). 68.8% with oral estradiol mean doses 17.18 $\pm$ 5.74 mg/week, 31.2% estradiol transdermal patch mean doses 45.15 $\pm$ 36.85 mg/week and 78.3% plus cyproterone acetate mean doses 52.13 $\pm$ 22.99 mg/day.Prior to treatment, prolactin levels (PRL) were 13.97 $\pm$ 9.33 ng/ml,estradiol(E2) 43.90 $\pm$ 30.27 pg/ml,testosterone(T2) 274.88 $\pm$ 215.41 ng/dL, LH 4.78 $\pm$ 5.51mUI/ml and FSH 5.16 $\pm$ 6.44 mUI/ml.After a mean follow up of 24.7 $\pm$ 35.6 months, PRL increased to 23.54 $\pm$ 14.19 ng/ml ($P = 0.02$),E2 to 48.89 $\pm$ 24.92 pg/ml ($P = 0.03$), T2 dropped to 111.25 $\pm$ 160.03 ng/dL ($P = 0.023$), LH to 2.01 $\pm$ 3.42 mUI/ml ($P = 0.021$) and FSH to 2.60 $\pm$ 4.34 mUI/ml ($P = 0.025$). None prolactinomas were reported.
Conclusion
Transgender females treated with estrogens have elevations in prolactin levels although any case of prolactinoma was reported.Clinicians should measure prolactin levels in transsexual people and perform imaging techniques of the pituitary in those patients with high prolactin levels.

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Neuroendocrinology

P976

Abstract withdrawn.

Paediatric endocrinology

P977

Association of placental thyroid hormone concentrations with congenital cryptorchidism

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The placenta is a highly specialized organ, which ensures nutrient uptake, waste elimination, provides thermo-regulation, prevents passage of some xenobiotic molecules and regulates the quantity of thyroid hormones (TH) necessary for the fetal development. It is known, that even minor changes in maternal TH levels, can alter the fetal growth. Several factors can modify TH levels during pregnancy. Among them, increasing evidences show that prenatal exposure to persistent organic pollutants (POP), such as brominated flame-retardants (PBDE), polychlorinated dibenzo-*p*-dioxins and furans (PCDD/F), and polychlorinated biphenyls (PCB), could disrupt the maternal TH regulation system. Some years ago, we investigated the association between some POP measured in placenta and congenital cryptorchidism [1–3]. Congenital cryptorchidism is a genital malformation that occurs in 2-9% of newborns and it is associated with decreased semen quality and higher risk of testis cancer. Several factors seem implicated in such pathology; however, the possible relationship between cryptorchidism and thyroid hormone levels during the uterine life in boys born with such malformation has been poorly investigated. The aim of this study was to analyze the level of thyroxine (T4), 3,3′,5-triiodo-L-thyronine (T3), 3,3′,5′-triiodo-L-thyronine (rT3) in 58 placenta samples (28 cryptorchid boys, 30 controls) using a LC-MS method recently developed in our group [4]. The samples were randomly selected at the end of the 3rd trimester and collected at birth. The entire placenta was homogenized prior analysis and stored at -20° C.

Results

No difference was detected in thyroid hormone values between the case and control group. No differences between the two groups with respect to maternal smoking, maternal age, BMI, and birth weight was found. Only a difference was seen in gestational age between case and control. Although no association of placental thyroid hormone levels with congenital cryptorchidism was found, for more complete overview, future study should include TH measurement in maternal and fetal placenta as well as in the cord blood.

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P978

Abnormal uterine bleeding in adolescents: experience of a single center

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Introduction

Abnormal uterine bleeding (AUB) refers to uterine bleeding that is excessive or occurs outside of normal cyclic menstruation. The most common cause of AUB in adolescents is anovulatory cycles due to immature hypothalamic-pituitary-ovarian axis. Additionally, endocrinological problems (hypothyroidism, hyperprolacitenemia, etc.) and bleeding disorders may cause AUB. The management of AUB begins with an assessment of whether or not the patient is hemodynamically stable and then proceeding with medical management based on etiology and the severity of anemia. The aim of the study was to assess etiological factors and treatment of AUB in adolescents in our clinic.

Method

We evaluated the clinical and laboratory features of 29 adolescents with AUB referred to adolescent outpatient clinic within 2 years of time. Hemogram, TSH, free T4, beta HCG, FSH, LH, E2, prolactin and von Willebrand factor antigen, prothrombin time, partial thromboplastin time measurement and pelvic ultrasonography were done in all patients. The severity of bleeding was assessed as mild(Hb: $\geqq$12 g/dl), moderate(Hb: 10–12 g/dl) and severe(Hb: $<$10 g/dl).

Results

The mean age of the patients at menarche and admission were 12.1 ± 0.9 (10.5–14.0) and 13.7 ± 1.6 (11.3–16.9) years respectively (mean time between them 1.6 ± 1.3 (0.0–4.9) years). 55% of the patients had heavy and irregular menstrual bleeding and 45% of the patients had heavy bleeding since menarche. The severity of bleeding was assessed as mild in five patients, moderate in four patients and severe in 20 patients. None of them were found to have a bleeding disorder and one patient had uterus didelphys. One patient with severe AUB had hypothyroidism. In 93% of the patients AUB was due to anovulatory cycles. 25 (86%) patients were treated with oral contraceptives. Three patients were treated with tranexamic acid and six patients had to be given erythrocyte transfusion due to hemodynamic instability.

Conclusion

The most common cause of AUB in adolescents is anovulatory cycles. Once hemodynamic stability is controlled and provided, the patient must be evaluated for severity of anemia, possible bleeding disorders and causes of AUB.

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P979

Breast hypertrophy (macromastia) in puberty: case report

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Background

Virginal breast hypertrophy is a rare benign disease. It is a condition of abnormal enlargement of the breast tissue and is characterized by rapid and excessive growth of one or two breasts during peripubertal period. This condition causes significal psychological and physical discomfort to affected adolescents, such as feeling embarrassed, inability to find appropriate clothes, suffering from back and shoulders pain, perhaps the appearance of kyphosis under the weight of the breasts.

Case report

12 year old girl presented to the Endocrinology Department of our University clinic with the complaint of intensive breast growth for the past 5-6 months. Menarche at age 11 years old, regular menstrual cycles. Hormone levels, such as Prolactin, LH, FSH, estradiol, were within the normal range. Ultrasound of the mammary glands was only significant for dilated ducts up to 2.0 cm and small

pelvis without any abnormal features. Within one month of observation, foci of necrosis appeared on the skin mammary glands, with progressive involvement of previously unaffected areas, causing significant pain and suffering. Despite normal hormonal evaluation, a progestin therapy with dydrogesterone at a daily dose of 20 mg/day was initiated. Despite the therapy, the growth of the mammary glands and necrosis continued, therefore the decision was made to proceed with a mastectomy with further mammoplasty at age 18.

Conclusions and follow up

When considering mastectomy in a teenager, an accurate diagnosis and rigorous treatment plan require a team approach, including pediatric, medical and surgical disciplines. Outcomes data are scarce as most available data are limited to small case series or case reports.

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Pituitary - Basic

P980

In vitro characterization and comparison of commercial GnRH antagonists

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Introduction

Hypothalamic gonadotropin releasing hormone (GnRH) regulates mammalian reproductive system. It binds receptors (GnRHRs) expressed in gonadotrope cells of anterior pituitary, regulating the synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). GnRHR is a G protein-coupled receptor (GPCR) coupled to Gαq/11 protein and, to a lesser extent, to Gαi/Gαs proteins, simultaneously activating Ca^{2+}, β-catenin signaling and mitogen-activated protein (MAP)-kinases. GnRHR ligands were developed to be used as GnRH agonists and antagonists.

Aim

The aim of this study is to compare three GnRH antagonists, Cetrorelix, Ganirelix and Teverelix, in modulating GnRH-induced intracellular signaling *in vitro*. To this purpose, dose-finding and kinetics were evaluated.

Methods

Experiments were performed in GnRHR-transfected HEK293 cells, and in the human derived neuroblastoma (SH-SY5Y) cell line, naturally expressing GnRHR. GnRH-induced intracellular Ca^{2+} increase and cAMP production were evaluated by BRET, while CREB and ERK1/2 phosphorylation by Western blotting, in the presence or in the absence of GnRH antagonists.

Results

Upon stimulation by increasing doses of GnRH (pM-μM range), intracellular cAMP and Ca^{2+} accumulation occurred in HEK293 cells transiently over-expressing GnRHR (cAMP $EC_{50} = 11.58 \pm 0.29$ nM, $n = 3$; Ca^{2+} $EC_{50} = 25.97 \pm 0.15$ nM, $n = 3$). Moreover, 1 μM GnRH treatment produced a rise in intracellular cAMP sustained over 50 min ($n = 3$) in transfected HEK293, while it resulted in no significant cAMP accumulation in SH-SY5Y cells expressing endogenous GnRHR ($P < 0.05$, one-way ANOVA; $n = 3$). In GnRHR-transfected HEK293 cells, Ca^{2+} increase induced by treatment using concentration of 3-fold the EC_{50} GnRH was suppressed by 1 μM of antagonists ($P < 0.05$, one-way ANOVA; $n = 2$), while no significant inhibition was detected at lower doses of Ganirelix and Teverelix (pM-nM range). Only 100 nM Cetrorelix prevented GnRH-induced intracellular Ca^{2+} increase ($P < 0.05$, one-way ANOVA; $n = 2$). nM concentrations of GnRH failed to induce CREB and ERK1/2 phosphorylation in transfected HEK293 cells and in SH-SY5Y cells.

Discussion

Cetrorelix, Ganirelix and Teverelix have different *in vitro* activity, evaluated in terms of GnRH-induced intracellular Ca^{2+} increase, suggesting that these drugs may act differently at the molecular level.

Conclusions

Since GnRH antagonists may be not equivalent *in vitro*, drug-specific effects *in vivo* should not to be excluded.

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Steroid metabolism + action

P981

Facial feminization/masculinization: the effect of hormone treatment in transpersons

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Background

Facial feminization or masculinization is particularly important in transpersons, both for self-image and social interaction. Females tend to have a smaller, rounder face, with more prominent cheeks and males tend to have a larger, more square face with frontal bossing. It is unknown whether cross-sex hormones can change these features. However, transgenders themselves often report facial changes due to hormone treatment. Therefore we aim to objectify if hormone treatment in transpersons can cause facial feminization and masculinization.

Design

In a single center cohort study, we studied persons diagnosed with gender dysphoria, transwomen and transmen, who were treated with a regimen of hormones according to protocol (estrogen and cyproterone acetate in transwomen and testosterone in transmen). 3D facial images were made with an Artec Spider scanner at baseline and after 3 months of treatment. The primary outcome was relative local shift of skin in millimeters after 3 months of treatment, measured in 22 soft tissue landmarks.

Results

We included 14 transwomen and 6 transmen, mean age 28.3(IQR 21.5–30.0 years). Face surface mappings (colormaps) in transwomen demonstrated a small shift of skin in the jaw and cheek region. The gonion landmark shifted towards the origin in the x-axis (mean = 1.19 mm; 95%CI, −0.46 to 2.43) and the cheek landmark shifted away from the origin in the z-axis (mean = 0.50 mm; 95%CI, 0.09 to 0.91). In transmen, the colormap showed a small increase in the cheek region, corresponding with a measured shift towards the origin in the z-axis (mean = −0.54 mm; 95%CI, −0.77 to −0.31).

Conclusions

In both transwomen and transmen the face shows changes in the first 3 months of treatment. In transwomen the shifts implicate a rounding of the jaw and an increase in cheek tissue. In transmen the shift implicates a decrease in cheek tissue. These changes suggest that hormonal treatment induces facial feminization in transwomen and masculinization in transmen. Furthermore, this research shows that 3D imaging is a promising tool for the evaluation of facial changes.

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P982

Polycythemia in transmen – Prevalence, determinants and outcome in a large cohort

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Introduction
Testosterone is known to have an effect on hematocrit levels, with polycythemia as an unwanted side effect. An increase in hematocrit levels is also seen in transmen after starting cross-sex hormonal treatment (CHT) with testosterone. The aim of this study is to investigate the effect of cross-sex hormonal treatment with testosterone on hematocrit levels in the context of the safety aspects of this treatment. The prevalence, determinants and outcome of secondary polycythemia were studied in a large cohort of transmen.
Methods
Adult female-to-male transpersons who started cross-sex hormonal treatment with testosterone and were monitored with laboratory control of hematocrit levels at our center were included. Polycythemia was defined as a hematocrit > 50%, measured at any moment in treatment. The prevalence of a hematocrit > 50% and > 54% and thrombogenic complications were studied. Determinants in the development of polycythemia studied were age at start of hormonal treatment, tobacco use, medical history, testosterone levels and type of testosterone admission.
Results
Of the 1218 patients included, 24.8% developed a hematocrit (Ht) > 50%, 4.2% had a maximum hematocrit of > 54% during the median 60 months of follow-up. The relative risk for smokers to develop a Ht > 50% was 1.27 (95% CI 0.90–1.78) and 1.67 (95%CI 0.84–3.34) for a Ht > 54%. Compared to testosterone gel, for injection with esters the OR for the development of a Ht > 50% is 2.00 (CI 1.30-3.08) and for a Ht > 54% 4.46 (CI 1.29–15.4). Compared with testosterone undecanoate, the OR is 2.12 (CI 1.25–3.63) for the development of a Ht > 50% and 4.12 (CI 1.01–16.9) for the development of a Ht > 54% respectively.
Discussion
Polycythemia is seen as a frequent side effect of testosterone admission in transmen. The number in thrombogenic complications was low. Tobacco use increases the risk of developing high hematocrit levels. Compared to testosterone gel, both injections, testosterone esters and testosterone undecanoate, increased the risk to develop polycythemia.

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P983

17-Beta hydroxysteroid dehydrogenase 3 deficiency: Three case reports

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Introduction
Deficiency of 17-βHSD3 is a rare autosomal recessive disorder of sex development manifesting in XY karyotype individuals. The presentation can range from partial or incomplete virilisation at birth to primary amenorrhoea and virilisation at puberty of an externally phenotypically female individual.
Case reports
Case1 A 2-year-old girl presented with ambiguity of external genetalia. She had no significant past medical or surgical history. On exam she had cliteromegaly measuring 2.5 cm and bilateral inguinal mass consistent with gonads (Prader stage4). Pelvic MRI showed inguinal testis, normal adrenal gland, a blind vagina and absent internal female structures. The serum testosterone (T) was 0.9 ng/ml and rose to < 3 ng/ml after HCG stimulation. The serum androstenedione(A) was 12 ng/ml (8–250). The T:A ratio was low 0.16 (< 0.8). The karypotype was XY. Gene analysis revealed a homozygous mutation of the 17-βHSD3gene, c618C > A. She underwent bilateral orchidectomy at at the age of 3, genitoplasty at the age of 8 and was commenced on oral estrogen. This resulted in satisfactory breast development and sexual intercourse was more comfortable. Case 2: (Cousin of the first patient) A 7-year-old girl presented with inguinal hernia. On exam she had cliteromegaly (Prader stage1). Pelvic ultrasound and MRI showed inguinal testis and absent internal female structures. The karypotype was XY and gene analysis showed the same mutation as the first case (heterozygous). Case 3: A 16 year old woman presented with primary amenorrhoea, poor breast development, hirsutism and cliteromegaly. She had increased hair growth on her abdomen and face as well as increased muscle mass and deepening of her voice. Pelvic ultrasound and MRI showed uterine and ovarian agenesis. The karypotype was XY. The serum testosterone was 2.82ng/ml. The serum androstenedione was high at 9.6 ng/ml (three times the upper limit of normal). The T:A ratio was 0.3 (< 0.8) after HCG stimulation. Diagnosis of 17-βHSD3 deficiency was confirmed with genetic mutation of the 17-βHSD3 gene.
Conclusion
We have described 3 patients with classic clinical and biochemical features of 17-βHSD3 deficiency in whom a mutation was identified in the 17-βHSD3 gene. Identification of affected individuals and molecular biologic studies may help elucidate the clinical conundrums of this disorder. For patients who have a female gender identity, management includes orchidectomy to reverse virilisation and to remove gonads with malignant potential. Estrogen replacement is provided to maximise female secondary sexual characteristics and to prevent bone loss.

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Thyroid (non-cancer)

P984

Relationship between hypothyroidism and androgen deficiency in men in different periods of mature age

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The aim of the present study is to determine the relationship between hypothyroidism and androgen deficiency in men of mature age.
Material and methods
60 men with primary hypothyroidism ranging in age from 21 to 60 years were studied. The men were divided into two age groups according to the periods of human ontogenesis – the group of the first period of mature age (from 21 to 35 years) and the second group of the mature age (from 36 to 60 years).
Results
Age-related changes in the hormonal status of the examined men in the first and second mature periods were related to the content of blood serum total and free testosterone. In the second period of mature age men, the content of total testosterone was 1.36 times lower and free testosterone – 1.54 times lower than in men in the first mature period. Reduction of testosterone levels in the older age group men were not accompanied by increased levels of gonadotropins in the blood. This fact may evidence the low sensitivity threshold of the pituitary-hypothalamic system to a decrease in the production of testosterone with age. In both men age groups with hypothyroidism the content of total testosterone in the blood serum was lower than in men without hypothyroidism. However, the influence of hypothyroidism was more expressed in men of the first mature period, in which the presence of hypothyroidism was associated with a decrease in the content of the hormone by 2.14 times. In addition the decreasing in this magnitude by 1.36 times was in men of the second period of mature age. The frequency of hypogonadism was 45.2% in men of the second period of mature age, including men without hypothyroidism – 32.9%, and with hypothyroidism – 61.7%. The correlation analysis established the presence of statistically significant ($P < 0.05$) feedbacks between the level of total testosterone and the values of indicators characterizing hypothyroidism.
Conclusions
The presence of hypothyroidism is associated with androgen deficiency in men of the second period of mature age in 60% of cases, but, in comparison with men of the first period of mature age, clinical features of androgen deficiency are more expressed in the second period.

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Poster Presentations: Thyroid

Clinical Case Reports - Thyroid/Others

P985

A silent thyroiditis in the remission period of Graves' disease

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Silent thyroiditis is characterized by the destructive thyroid inflammation and is considered to be a chronic autoimmune thyroid disease, although the etiology could not have been fully explained. On the other hand, Graves' disease is autoimmune phenomena as well as silent thyroiditis and silent thyroiditis has been classified as part of the spectrum of Graves' disease. Although, the thyroid stimulating antibody (TSAb) are found positive in most of Graves' disease but rarely in silent thyroiditis cases and the role of TSAb in the pathogenesis of these diseases has still been unknown. In this case report, we aimed to present a rare case in which repeated thyrotoxicosis as a silent thyroiditis was followed by Graves' disease. A 40 year old woman admitted to outpatient clinic with the complaint of palpitations, sweating and weight loss 3 years ago. Laboratory results were TSH: 0.005 μIU/ml (normal:0.56–5.57), sT3: 8.5 pg/ml (normal:2.3–4.2), sT4: 4.05 ng/dl (normal:0.93–1.7) and anti-thyroid peroxidase and anti-thyroglobulin antibodies were positive. Thyroid scintigraphy showed homogeneous increased uptake involving the whole thyroid gland and the patient was diagnosed with Graves' disease. Treatment of the patient with propylthiouracil was stopped at the 18th month of treatment. After the 18 months of untreated follow-up, she was referred to our hospital with complaints of palpitation, tremor and sweating. On the physical examination of the patient the painless thyroid gland was palpable. Laboratory findings were as follows; TSH: 0.006 mU/l, sT3: 3.54 ng/l, sT4: 1.6 ng/dl and ESR was normal. Thyroid scintigraphy revealed a decreased uptake in the thyroid gland. The patient was diagnosed with silent thyroiditis and propranolol was started for symptoms. One month later, laboratory findings were TSH: 10.08 mU/l, sT4: 0.894 ng/dl, sT3:2.59 ng/l and the propranolol therapy was withdrawn and low-dose levothyroxine therapy was started. In a study with the patients who were followed up Graves' disease in remission that developed thyrotoxicosis during pregnancy and postpartum period, postpartum thyroiditis was diagnosed in 44% of patients, and 28% of patients were evaluated as Graves' exacerbation. Although the relationship between Graves' remission and silent/postpartum thyroiditis is not fully demonstrated. In conclusion, other thyrotoxicosis causes should be excluded before the patient is accepted as Graves' recurrence after the thyrotoxicosis in patients who are followed up due to Graves' disease in remission.

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P986

Amyloid goiter secondary to rheumatoid arthritis

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Introduction
Amyloidosis refers to a variety of conditions in which amyloid proteins are abnormally deposited in organs and/or tissues. Clinically significant enlargement of the thyroid owing to amyloid deposition is a rare occurrence.
Case report
58-year-old female referred to endocrinology clinic presenting with increasing dyspnea, dysphagia and visible swelling at the base of the neck for the last 6 months. She had been diagnosed with rheumatoid arthritis six years ago but had not used the prescribed medication regularly; she is on regular nonsteroidal anti-inflammatory drugs. Physical examination revealed: BP, 130/70 mmHg; HR, 100 bpm; RR, 22/min. Temperature, 37°C. Enlarged thyroid gland firm in consistency with multiple nodules on palpation. Laboratory test results included: TSH, 1.24 IU/dl (normal range, 0.4–4.0); free T3,2.2 ng/dl, free (N,2.3–4.4) free T4, 1.21 ng/dl (normal range, 0.7–2) glucose, 90 mg/dl, albumin; 3.6 g/dl, creatinine, 1.7 mg/dl; 24-h proteinuria, 1.9 g/day. Both of the thyroid lobes are enlarged in the ultrasound examination. The right lobe showed multiple nodules of 45–50 mm size, with areas of cystic degeneration. Renal ultrasound examination revealed grade II nephropathy. Echo heart showed impaired left ventricular filling, sclerotic aortic valve, and normal ejection fraction.Because of compressive symptoms, a computed tomography (CT) scan was performed before surgery, showing multinodular goiter with no tracheal compression. Total thyroidectomy was done Microscopic study of the specimen showed extensive infiltration of thyroid parenchyma by an amorphous expansive amorphous eosinophilic substance deposition and lipid infiltration in the whole thyroid gland. On Congo red dye staining, amyloid deposition was stained red in the interstitial space and it showed an apple-green birefringence with the polarizing microscope with no neoplastic cells. Renal biopsy was performed due of kidney involvement, showing kidney infiltration by amyloid with marked tubulo- interstitial fibrosis.
Conclusion
Amyloid goiter is an atypical presentation of an already rare disease. A high index of attentiveness should be kept whenever amyloid deposits are seen on fine needle aspiration cytology, as they are also established in medullary carcinoma. The confirmative diagnosis rested on the histopathology of the specimen.

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P987

An uncommon but serious hematological manifestation of Grave's disease: Grave's disease induced bicytopenia

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Graves' disease (GD) is a common cause of hyperthyroidism. Associated hematological complications rarely occur. Most review articles describe it as a rare manifestation and often reported as isolated cases or series. These disorders in hyperthyroidism may stem from the primary thyroid pathology or its treatment. In untreated primary hyperthyroidism, effects on hematological parameters range from mild single lineage involvement to pancytopenia. The most feared treatment related hematological disorder is drug induced agranulocytosis. We present a middle-aged gentleman with 10 year's history of GD. Over the last 2 years, he had repeated admissions for severe thyrotoxicosis, sepsis and recurrent pancytopenia. In end 2014, he was admitted for an episode of neck cellulitis. He was floridly hyperthyroidism and had developed new onset bicytopenia – leucopenia (neutropenia) and thrombocytopenia. He had stopped taking his regular dose of Carbimazole 30 mg OM for the last 2 weeks. The bicytopenia was unlikely drug-induced agranulocytosis due to his non compilance. A multidisciplinary team was involved including endocrinology, hematology and nuclear medicine. An attenuated dose of Carbimazole 20 mg daily was restarted with close monitoring of his cell counts. Cholestyramine was added as an adjunct. Granulocyte-colony-stimulating-factor (GCSF) injections were initiated to boost the neutrophil counts. The patient also underwent a bone marrow examination (BME). The BME showed quantitatively adequate granulopoiesis with normal neutrophil count and increased megakaryopoiesis. The mildly hypercellular marrow with adequate hematopoiesis in all 3 cell lines suggested that the ongoing neutropenia and thrombocytopenia is secondary to peripheral consumption and destruction. Carbimazole induced agranulocytosis would result in a hypocellular marrow. Thus, the most evident cause of the bicytopenia was an autoimmune cause from hyperthyroidism. The patient's neutrophil and platelet counts improved as he achieved an improved thyroid state. This improvement of cell counts together with his thyroid status further reinforced the hypothesis of hyperthyroidism induced bicytopenia. The patient discharged well with an outpatient appointment for definitive therapy with radio-iodine ablation. However, he remained poorly compliant. This resulted in three further admissions for similar presentations of sepsis, florid hyperthyroidism and bi- or pancytopenia. His recovery of his cell counts would always mirror the improvement of thyroid status. He eventually received two doses of RAI 6 months apart. Mr N responded adequately to the 2nd dose of RAI therapy. At 8 weeks' mark, he was euthyroid status. The hematological abnormalities had fully resolved along with this.

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P988

A rare cause of subclinical hypothyroidism: macro-TSH

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Macro TSH is a large molecular-sized thyroid-stimulating hormone (TSH) that is including TSH and anti-TSH antibody. Patients with macro TSH have elevated serum TSH and normal free thyroxine levels similar to subclinical hypothyroidism. A 18-year old female patient was referred from gynecology and obstetrics to endocrinology clinic for evaluating of elevated TSH with normal free thyroxine levels. Laboratory and clinical investigations revealed that only discordant TSH levels (normal reference range: 0.25–4.2 μIU/ml; two times separately checked results; 5.65 μIU/ml; 5.47 μIU/ml; respectively) with electrochemiluminescence immunoassay method with no other any demonstrable hormonal or clinical findings. On admission to our endocrinology department, she was clinically euthyroid. She had no history of medication or ilness. The patient had normal thyroid ultrasound pattern with tested mildly positive for both thyroglobulin and thyroid peroxidase antibodies. Rheumatoid factor, which can act like heterophile antibodies, was undetectable in this patient. Polyethylene glycol (PEG) method for TSH measurement was planned to find out the macro-TSH. We have used the same blood samples which of the TSH levels were found to be high, while using the PEG method was found to be within normal ranges as 1.50 mIU/L (5.65 μIU/ml to 1.50 μIU/ml; decrease of 75%) and 1.26 mIU/l (5.47–1.26 μIU/ml, decrease of 77%); respectively. The TSH value was exhibited to be markedly low by PEG precipitation test in our patient that she had PEG-precipitable TSH ratios greater than 75% as well as it's supposed to be reported by Hattori et al study. Macro-TSH should be kept in mind in patients with high TSH levels without symptoms of hypothyroidism in the differential diagnosis before unnecessary investigations and treatment.

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P989

Manifestation of thyrotoxic crisis after delivery: clinical case report

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Thyrotoxic crisis is a manifestation of an extreme and rare state of thyrotoxicosis. It is an acute, life-threatening state. The mortality of thyrotoxic crisis is currently reported at 8–25% [1]. The clinical presentation includes fever, tachycardia, hypertension followed by congestive heart failure, neurological and mental disorders. We present a case of 34-year-old woman without any history of thyroid hyperactivity. She was admitted to hospital after premature amniotic fluid leakage in 34th week of her second pregnancy and complained of intensive dyspnoe. After patient full examination it was decided to deliver the baby by Caesarean section because of progression of cardiopulmonary failure (her heart rate was 156 bpm, blood pressure 181/91 mmHg, respiratory rate 44 bpm, O_2 saturation 91%, ejection fraction was 30%). After section her condition remained critically serious and she moved to intensive care. Her respiratory failure required ventilatory support for 11 days, she had fever (T 39.6 °C), uncontrolled tachycardia and hypertension despite treatment. Although she was initially thought to have severe preeclampsia with pulmonary oedema complicated pneumonia, but her thyroid function tests indicated severe thyrotoxicosis: TSH <0.01 (normal 0.4–3.6 mU/l), free T_3 35.35 (normal 3.34–5.14 pmol/l), free T_4 82.58 (normal 9–21.07 pmol/l). This clinical picture was consistent with a diagnosis of thyrotoxic crisis. Treatment was started with thiamazole 80 mg/d, intravenous hydrocortizone 200 mg/d, Lugol's iodine 5% 20–30 drops/d, propranolol 160 mg/d and supportive care. Despite thyroid decreasing function, 7th day after section patient state remains difficult and it was decided to increase thiamazole dose to 120 mg/d, hydrocortizone to 300 mg/d and change propranolol to metoprolol 200 mg/d. Following 2 weeks on intensive care she made a remarkable recovery. She was discharged home on the 32nd postoperative day with a healthy baby. Now she is on endocrinologist control, her last anti-TPO was 2354 (normal 0–12 kU/l), anti-Tg 51 (normal 0–100 kU/l), anti-TTH 15.2 (normal <9 U/l). Thyroid ultrasound – thyroid gland was enlarged, hypoechogenic and heterogeneous structure because of hypoechogenic zones. According to test results it was diagnosed Graves' disease. It is almost one year after thyroid storm, she still has persistent subclinical hyperthyroidism despite consistent treatment with thiamazole. So, we are considering thyroidectomy. Reporting this case we want physicians to be aware of this rare situation as symptoms of thyrotoxic crisis are similar to those of preeclampsia.

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P990

Sunitinib induced myxedema in a patient with metastatic gastrointestinal stromal tumor (GIST)

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Introduction
It is known that hypothyroidism has multiple etiologies including tyrosinkinase inhibitors (TKI) agents which can cause thyroid disfunction through different mecanisms, not fully defined yet- Vascular endothelial growth factor receptor (VEGFR) blockade, thyroiditis, iodine uptake blockade, increased activity of deiodinase 3, increased hormone clearance. Some recent trials suggest that there is a correlation between the incidence of hypothyroidism and the outcome of patients treated with TKI, therefore the occurrence of hypothyroidism during Sunitinib treatment is a predictive marker of a progression-free survival.
Case report
We report the case of a 62-year-old female, with a family history of hypothyroidism (daughter- Hashimoto's disease). The patient was diagnosed in 2007 with metastatic retroperitoneal tumor GIST and since 2010 she has been treated with Sunitinib. She was first referred to our Institute in June 2017, after being diagnosed with pericarditis (medium pericardial effusion, without cardiac tamponade). The patient complained about gaining weight (7 kg in the past few months), extreme fatigue, palpebral edema, dry skin and cold intolerance. The hormonal profile found a TSH level = 69 μUI/ml (normal range = 0.5–4.5) with FT_4 = 3.84 pmol/l (normal range = 10.3–24.4) and a negative ATPO. Biochemical tests revealed hypercholesterolemia (cholesterol = 227 mg/dl), hypertrigliceridemia (trygliceride = 258 mg/dl), increased serum creatinine level (creatinine = 1.63 mg/dl), moderate anemia (hemoglobin = 10.1 g/dl), neutropenia (1.6×1000/ul) and high inflammatory markers (VSH = 65 mm/h). Thyroid ultrasound revealed a typical pattern for atrophic thyroiditis and a group of macrocalcifications in the left lobe. We initiated the treatment with 37.5 μg levothyroxine for the first 10 days, then progressively raised at 50 μg/day for the next 14 days; then to 62.5 μg/day, 75 μg/day, 87.5 μg/day until the dosage of 100 μg/day, with a decline in TSH from 69–1.55 μUI/ml and an improvement in renal function from a 1.63 mg/dl creatinine level to 0.85 mg/dl. Also, the pacient has a good response to Sunitinib, based on the long progression free survival (2010–2018).
Conclusion
Hypothyroidism induced by Sunitinib is a common side effect of the molecule. It is important to recognize it in a patient who is being treated with TKI in order to prevent possible complications. In addition, this case report comes to strengthen some recent opinions regarding a longer progression free survival in patients who develop hypothyroidism during treatment with Sunitinib.

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P991

Tuberculosis abscess resembling thyroiditis

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Tuberculosis (TB) infection incidence is still high among solid organ transplant recipients. TB in recipients can manifest several years after transplantation, especially in developing countries. Atypical clinical presentations and extra-pulmonary involvement are not uncommon in recipients. Herein, we reported a kidney transplant recipient with TB abscess who admitted with fever and swelling on thyroid gland region.

Case

A 57-year old female recipient underwent a successful deceased kidney transplantation 4 years ago. She applied to our outpatient clinic with fever and swelling on the thyroid gland region. She complained fever for 20 days without sweating and tender swelling with hyperemia in front of her neck. On physical examination there was only hyperemic, hard, fixed, 6×8 cm diameter swelling in the midline of the neck which was enlarged to the right side. The laboratory tests revealed neutrophilic leukocytosis (15.0 K/mm^3), elevated CRP (23.7 mg/dl), creatinine (1.5 mg/dl) and PTH (698 pg/ml); low 25-OH vitamin D (<8 µg/l), calcium (8.3 mg/dl) and TSH (0.269 µIU/l); normal free T4 (1.2 ng/dl) and thyroglobulin (32 ng/ml) levels. Ultrasonography revealed hypoechogenic nodular thyroid gland and a 7.5×7 cm heterogeneous cyst. Neck computed tomography showed a 7.5×7 cm diameter abscess on the right cervical region extending to the upper mediastinum. Thyroid and parathyroid scintigraphies (Tc-99m pertechnetate + Tc-99m MIBI) revealed that the mass was unrelated to these glands. Secondary hyperparathyroidism due to vitamin D deficiency was diagnosed. Empirically meropenem and teicoplanin were administered. The drainage of the abscess was performed with micropuncture. Because of the mediastinitis risk the abscess was drained totally. Mycobacterium tuberculosis was detected with polymerase chain reaction of suppurative drainage material. A four-drug regimen with isoniazid, rifampycin, ethambutol and pyrazinamide was initiated. The abscess resolved and she was discharged with anti-tuberculosis regimen and immunosuppressive drug dose arrangement.

Conclusion

Extrapulmonary or disseminated TB infection rate after transplantation is 30–50%. Although TB occurs within the first year of the transplantation in 95% of the cases, it may appear late as in the present case. Extrapulmonary TB infection should be kept in mind in recipients with atypical suppurative lesions in thyroid region as was the case in our patient.

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P992

Significant cardiac disease complicating Graves' disease in the young

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Introduction

Graves' disease (GD) is associated with cardiac complications like tachydysrythmias, coronary ischaemia and cardiomyopathy. They are uncommon in the young. We present three individuals without previous cardiac disease, who developed significant cardiac complications of GD.

Case presentations

Subject 1

A 34-year-old female smoker, presented with breathlessness, palpitations, tremors and agitation for several weeks. Her fT4 was 98.4 (11–25 pmol/L), fT3 46.9 (3.1–6.8 pmol/L), TSH<0.01 (0.27–4.2 mU/l) and thyrotrophin receptor antibody (TRAb) 34.8 (<0.9 U/l). A thyroid storm was diagnosed, and she was given carbimazole, betablockers, steroids, antibiotics and intravenous fluids. A few days later, she became breathless and on echocardiography, cardiomegaly and pericardial effusion (2.9 cm) was seen, despite improving thyroid function (fT4 27.8; fT3 12.8). She had steroids and nonsteroidal agents with good response. There were no other identifiable causes for her pericardial effusion.

Subject 2

A 28-year-old previously fit male presented with weight loss, palpitations, sweating and diarrhoea, with a goitre and bruit. His fT4 was 38, fT3 13.9, TSH< 0.01 (abnormal for over 6 months) and TRAb 9.3. He was given carbimazole, but one month later presented with acute heart failure (HF) despite improving thyroid function. Echocardiography revealed severe dilated cardiomyopathy (DCM) with an ejection fraction (EF) of 12% and lisinopril, bumetanide, epleronone and ivabradine were given. Echocardiography 4 months later (when euthyroid), showed improvement in EF to 21%. Further investigations (including angiography and MRI) ruled out other causes for DCM. He awaits thyroidectomy.

Subject 3

A 42-year-old previously healthy woman presented acutely with palpitations, breathlessness and leg swelling, and was found to be in fast atrial fibrillation and HF. She had been thyrotoxic for several months (free T4 54.3; free T3 >46.1; TSH <0.01; TRAb 4.5) and had bisoprolol, digoxin, propylthiouracil and HF treatment. Echocardiography at presentation showed cardiomegaly, pleural effusion, and EF of 29%. Myocardial perfusion scans did not show inducible ischaemia. She had early total thyroidectomy and remains in sinus rhythm with EF of 50%.

Conclusions

Significant cardiac complications of GD (pericardial effusion, DCM, and tachycardiomyopathy) may occur in fit young patients without previous cardiac disease, who usually have had thyrotoxicosis for several months. There should be a high index of suspicion in those who remain symptomatic despite control of their thyrotoxicosis. Though the majority of patients respond well to thionamides with reversal of cardiac abnormalities, definitive treatment should be discussed early to avoid GD relapse and a recurrence of cardiac decompensation.

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P993

Thyroiditis in patients with rheumatoid arthritis, related to rituximab

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Introduction

Rituximab is indicated in patients with active rheumatoid arthritis (RA), which through the Fab domain, binds to the CD20 antigen on the surface of B lymphocytes, generating lysis of B cells, present in the thyroid, by cytotoxicity dependent on complement, as a result of the binding of C1q, mediated by the Fc domain, destroying the thyroid follicles, by infiltration of inflammatory cells (1) (2).

Objective

Describe the characteristics of patients with RA who presented thyroiditis, after treatment with rituximab.

Methods

Descriptive study case series. We reviewed 4 clinical histories of patients with RA with therapeutic failure to DMARDs and anti TNF, without previous autoimmune thyroiditis, from a high complexity clinic in Cali, Colombia.

Results

Three patients were women, median age was 50 years (37–61), DAS28 3 (3–5), CRP 15.5 (8–28), ESR 78 (55–120), TSH 0.095 (0.01–0.2), T4L 2 (2–4), thyroid antiperoxidase antibodies 235 (92–800), and thyroiditis evolution time of 2.5 months (1–4). All had diffuse goiter by ultrasound and the scintigraphy was hypocaptant, none had a history of respiratory tract infection; they reported odynophagia and malaise. The 4 patients received management with steroid and 2 with beta-blockers. At 8 months they presented symptom improvement and complete resolution (DAS28 1 (1–3), TSH 0.9 (0.6–1.2), T4L 1.095 (1–1.3)).

Discussion
Biological agents can induce autoimmune phenomena, the evidence so far with rituximab is limited (3). Hyperthyroidism can be explained by an increased activation of thyroid peroxidase (TPO), enzyme that catalyzes reactions for the synthesis of T3 and FT4. A plausible explanation for the elevated TPO activity is a drop in the level of antibodies against TPO by rituximab-induced depletion of plasma cell precursors has been described in the literature and differs from Graves' disease by lowering uptake in the scintigraphy (4). We observed in our patients complete resolution with tests of normal thyroid function at 8 months, probably due to recovery of B cells. It has been described that the B cell count in peripheral blood, begins to increase from week 24 and evidence of repopulation is observed in most patients, at week 40 (5).
Conclusions
Treatment with rituximab could be related to the presentation of thyroiditis in patients with active RA.
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P994

Pericarditis: uncommon onset of anti-neutrophil cytoplasmic antibody-associated vasculitis induced by methimazol
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Introduction
Anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis drugs induced are a rare side effect of antithyroid drugs. It is more commonly associated with propylthiouracil (PTU). The clinical manifestations are polymorphic like in primary vasculitides, but less severe; ranging from less specifics syndromes to multiple organs injured and lifethreatening in rare case. Cardiac involvement is uncommon. Herby we present the first case report of a 25-yr-old woman wich developed a syndrome of pericarditis as the first sign of ANCA associated vasulitis induced by methimazol.
Observation
A 25-yr-old woman was admitted with a recent history of dyspnea. A Graves' hyperthyroidism was diagnosed 1 year before; she was clinically and biochemically euthyroid on Methimazol 20 mg daily 1 year before. The examination revealed blood pressure of 120/60 mmHg, pericardial rub, and no edema. GFR $>$ 60 ml/min/1.73m, and systemic/urine sediment showed no abnormalities. The chest radiography showed severe cardiomegaly. An echocardiography showed a moderate-to-severe pericardial effusion. Direct Coombs test was negative, C3 and C4 within the normal range, ANA was negative, ANCA was positive (1/300), with a p-ANCA pattern. Cryoglobulinemia was negative. Treatment was started with doses of steroids at 1mg/kg/day, and the patient's state start to improve considerably. Two days after her admission, she developped necrotic-looking vasculitic skin lesions on bilateral lower extremity and on her right ear. Skin biopsy showed leukocytoclastic vasculitis. The methimazol induced vascularitis was suspected, so we stopped the offending treatment. In her follow up, we noticed a progressively disappearance of the skin lesions and pericardial effusion. In the light of clinical and laboratory findings she was diagnosed leukocytoclastic vasculitis caused by MMI, with positive p-ANCA.
Conclusion
The importance of this case is to call attention to the possible occurrence of pericarditis as a first symptom of methimazol-induced ANCA vascullitis.
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P995

Coexistence of hashimoto thyroiditis and De Quervain's thyroiditis
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Introduction
De Quervain's Thyroiditis (DQT) is a self-restriction inflammatory disease of the thyroid gland that presents severe pain localized in the neck. But few cases of a painful variant of Hashimoto's thyroiditis (HT) have been described as well. Thyroid ultrasound (US) may reveal in homogeneous hypoechoic pattern in both conditions.
Case
A 51-year old woman was admitted to the Hospital of Lithuanian University of Health Sciences, Kauno klinikos with the pain in anterior region of the neck and throat. Laboratory tests: erythrocyte sedimentation rate (ERS) 34 mm/h (normal 0–13), C-reactive protein 3.82 mg/l (0–10), TSH 0.11 mIU/l (0.27–4.2), FT4 17.95 pmol/l (12–22), FT3 4.2 (3.34–5.14), anti-TSH-R 3.9 U/l ($n<9$), anti-TPO 7 kU/l (0–12), anti-Tg 316 kU/l (0–100). US revealed decreased echogenicity, nonhomogeneous thyroid parenchyma and heterogeneous hypoechoic focal areas in both lobes. The treatment with nonsteroidal anti-inflammatory drug (NSAID) was started with gradually reduced dose. However, mildly elevated ERS and suppressed TSH remained. US showed the same size of focal area 2 months later. For the differential diagnosis (DD) of thyroid cancer (TC), painful HT and DQT coexisting with HT, fine needle aspiration biopsy (FNAB) was performed. FNAB showed changes compatible with DQT. It was decided to continue the treatment with NSAID and prednisolone was prescribed while gradually reducing the dose. The patient's condition has improved significantly. During follow-up appointment, after 3 months, thyroid hormones were in normal range and US showed decreased size of heterogeneous hypoechoic focal areas in both lobes.
Conclusions
Coexistence of DQT and HT is very rare and the diagnosis can be challenging. Clinical manifestation and ultrasonography results may be similar in both conditions. FNAB may be required for DD. The complete establishment of US patterns may last for one or two years.
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P996

Tea and juice as a causes of levothyroxine malabsorption and intermittent hypothyreoidism: a case report
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Introduction
Biological casuses of levothyroxine (LT4) malabsorption are well known. Congestive heart failure, gastrointestinal diseases, pregnancy, medication or dietary interference are the most commonly known causes of poor oral absorption of LT4. However, when substitution therapy with LT4 fails we need to be more exploratory.
Case description
Female, born in 1987, BH 164 cm, BW 73kg, in 2010 she was presented as M. Basedowi and in october 2011 near thyreodectomy was done. In 2012 despate 200 mgr LT4 her TSH had been always elevatred. She was admitted to hospital in december 2017 with levothyroxine dosage of 700 mgr. In the last few months she was treated with Novothyral preparation 100, 3 tablets per day (combination of levothyroxyn 100 mgr and liothyronin 20 mgr) but without success. During 6 years period patient did have 24 controls (four per year) by secondary ot tertiary level endocrinologists). Most of the time she has been felt, briefly described, not healthy''. In 2014.y. and 2016.y. she had two birds. During pregnancy levothyroxine dosage was 300-400 mgr. During all these years transient hypothyreoidism has been presented. Values of hormones were as follows:

	Admittance to Clinic	7.day in Clinic	Average $\pm$ SD	Median	MIN-MAX.	Reference values
TSH mIU/L	$>$100	9.4	55.7 $\pm$ 61.97	23.8	0.01-201	0.35-4.94
fT4 pmol/L	5.9	10.8	12.8 $\pm$ 7.8	11.4	1.98-31.8	9-19
fT3 pmol/L	-	7.4	3.8 $\pm$ 2.2	3.57	0.2-8.8	2.6-5.7

On 8.day of hospitalisation we performed:

Table: Levothyroxyne Absorption Test (LAT) with 1000mgr levothyroxine

	0.h	1.h	2.h	3.h	4.h	5.h	Reference values
TSH mIU/L	4.15	3.77	3.52	3.36	2.65	3.05	0.35-4.94
-relation to 0.h	1	0,91	0,85	0,81	0,54	0,73	
fT4 pmol/L	12.1	16.86	23.91	24.26	26.76	22.48	9-19
-relation to 0.h	1	1,39	1,96	2,00	2,21	1,86	
fT3 pmol/L	7.4	7.35	7.67	7.43	7.6	6.97	2.6-5.7
-relation to 0.h		0,99	1,03	1.00	1.03	0.94	

After the test we obtained the data that she was taking levothyroxin on empty stomac but frequently with juice or tea. After a few days of hospital stay she started using the drug with water. Her latest dosage of levothyroxine is 100 mgr and latest control of hormones in referente range.

Discussion

LAT in our testing excluded malabsorpition of levothyroxine. Pseudomalabsorption was not caused because of nonadherence. Our patient did have actually dietary interference of juice and/or tea of mint with levothyroxine absorption.

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P997

Thyroid-type malignancies in struma ovarii and thyroid gland of two different origins: case report

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Introduction

Struma ovarii (SO) is a rare ovarian tumor that occurs as part of a teratoma or is found in serous or mucinous cystadenomas and consist of more than 50% thyroid tissue. More uncommon is to diagnose thyroid cancer in struma ovarii and thyroid gland of two different origins. We present a case of follicular thyroid carcinoma arising in struma ovarii of the right ovary and papillary thyroid gland carcinoma.

Case

A 70-year-old woman admitted to gynecology department with abnormal vaginal bleeding. Endometrial biopsy revealed endometrioid adenocarcinoma (G3). Abdominal computed tomography (CT) showed 10.3×7.6 cm cystic tumor arising from the right ovary. Also, multiple uterine myomas and 2.1×2.0 cm left adrenal adenoma were observed in the CT. Total hysterectomy and bilateral salpingo-oophorectomy with pelvic-aortic lymphadenectomy were performed. The histological examination reported vascular invasive with the restricted cellular growth within the capsule follicular thyroid carcinoma of the right ovary and confirmed endometrioid adenocarcinoma (G3) of the uterus body. External pelvic radiotherapy was used postoperatively, but systemic chemotherapy for uterus adenocarcinoma was not prescribed because of co-morbidities. Thyroid ultrasound showed multi-nodular goiter and thyroglobulin level was normal – 19.3 μg/l (0 – 50). Considering the possibility of synchronous tumor of thyroid gland patient underwent total thyroidectomy. Histopathological examination revealed papillary thyroid carcinoma in 3 mm and 5 mm size masses and on immunohistochemistry positive expression of CK - 19. A radiation oncologist decided not to administer radioiodine therapy as an adjuvant treatment because of a minor risk for recurrence. Adrenal adenoma was evaluated by the incidentaloma algorithm and no hormonal activity was detected. In her medical history, she had acoustic neurinoma operation and postoperatively uses small doses of bromocriptine because of hyperprolactinemia. Genetic analysis was performed but neurofibromatosis type 2 diagnosis and other genetical disorders were not approved. No further treatment was deemed necessary at this time and the patient was scheduled for follow-up.

Conclusion

There is no consensus about SO diagnosis and management in the literature because of its rarity, representing only 1% of all ovarian tumors. Therefore, it is important to remember that some of SO are associated with thyroid-type carcinoma and this may significantly alter patient management. Thyroglobulin measurement could be used as one of the follow - up markers evaluating the recurrence. Recurrences may be detected using iodine - 123 scanning, and repeat radioiodine ablation can lead to higher rates of survival.

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P998

Type 1 diabetes mellitus and sorafenib: coincidence or consequence?

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Introduction

Differentiated thyroid carcinoma is usually associated with a good prognosis. However, some of these tumors (5%) are radioiodine refractory and have different progression, associated with poor prognosis. In these situations, some tyrosine kinase inhibitors (TKI) can be used. We present a clinical case showing the difficulties in the follow-up and treatment of these patients.

Clinical case

A 60 years old woman, with a "multicentric papillary cancer, with high cells", underwent total thyroidectomy in 2000, followed by I131 ablation. TG remained undetectable but TgAb progressively higher. In 2005, lymph node cervical metastases were excised. In February 2017, Tg was still undetectable with TgAb 773 UI/ml and the 18 FDG-PET showed: "Bilateral hypermetabolic pulmonary metastases". She started sorafenib (800 mg) in September and 4 weeks later, she presented at the emergency service with a diabetic ketoacidosis (glycemia – 895 mg/dl; pH - 6,99), and was treated with intravenous fluids and continuous insulin infusion. After stabilization, she performed blood tests: A1C - 16,2%; GAD-65 Ab - 4,48 U/ml (<1); IA-2A Ab - 2,87 U/ml (<1). As the presence of different autoantibodies suggests the diagnosis of polyglandular autoimmune syndrome (PAS), we're waiting for the results of blood tests to exclude other autoimmune diseases. Meanwhile the level of TgAb reduced (350 UI/ml) but an urticaria reaction to sorafenib forced its reduction to 200 mg and later it was stopped. She is starting now lenvatinib.

Discussion

We present a patient with a papillary carcinoma and PAS who underwent a serious clinical manifestation of type 1 Diabetes (ketoacidosis) a few weeks after starting sorafenib. There's some evidence about the possible effects of TKI in immunologic reactions and autoimmunity. So, we can't exclude that this manifestation of DM could be a possible effect of this drug.

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P999

Thyroid arterial embolization for the treatment of large multinodular goiter and hyperthyroidism

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Background

Although hyperthyroidism has many treatment options, hyperthyroidism is difficult to control in some patients. Hyperthyroidism has three main treatment

options: antithyroid drugs, radioactive iodine therapy and surgical treatment. However, in some cases none of these treatments can be used. However, there are some patients who failed to respond to radioactive iodine therapy, patients who choose not to receive any one of the options, and others who are poor surgical candidates. Thyroid arterial embolization can be used for the treatment of Graves' disease and other thyroid conditions requiring thyroid ablation. We describe the case of a patient with a large multinodular goiter that was with thyroid arterial embolization.

Case

Fifty six years old man has admitted to our hospital complaints of fatigue, dyspnea, growing cervical mass and swallowing difficulty. When the patient's anamnesis was taken, it was learned that 20 years ago, the patient had subtotal thyroidectomy due to a nodular goiter. Patient who had not been followed for a long time, because of the current complaints increased in the last 2–3 months. On physical examination he presented a large, firm multinodular goiter that occupied the entire anterior cervical area. At admission, laboratory tests revealed normal sT4: 1.17 ng/dl (Normal Range: 0.89–1.37) and sT3: 2.45 pg/ml (Normal Range: 2.25–3.85), and decreased TSH: 0.017 μIU/mL (Normal Range: 0.47–3.41) levels. On ultrasound, a large goiter was visualized with multiple nodules of different sizes in both lobes. Thyroid scintigraphy showed irregular uptake with a large thyroid gland. Fine-needle aspiration biopsies performed in nodules were reported to be negative for malignancy. On neck computed tomography (CT) scan, the thyroid gland extended to the mediastinum and compressed the trachea. The patient was offered surgery because of symptoms of compression and extension of the gland to the mediastinum. Because the patient did not accept the operation, it was decided to thyroid arterial embolization to the patient. After embolization, no fever developed but the patient complained of mild anterior neck pain that regressed after therapy with standard anti-inflammatory treatment. At 30 days after embolization, thyroid hormone levels normalized and the thyroid ultrasound can showed that the thyroid gland had shrunk. The patient's complaints have improved substantially.

Conclusion

Thyroid embolization may be the treatment of choice in large multinodular goiter where the surgery is not accepted or the surgery is contraindicated.

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P1000

Thyroid hormone resistance and pituitary macroadenoma: is there a connection? – case report

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Introduction

Inappropriate secretion of TSH, despite elevated levels of T4, is due to either a TSH-secreting adenoma (TSHoma) or thyroid hormone resistance (RTH). RTH is a rare disorder, usually caused by mutations in the thyroid hormone receptor beta, characterized by a variable tissue hyporesponsiveness to thyroid hormone. The increased level of TSH may predispose to thyrotroph hyperplasia and possible adenoma formation.

Case report

A 21 years old female patient adresses for the first time in 2011 for primary amenorrhea. The clinical features like short stature (−2.3DS), obesity, round face and short fourth metacarpal, along with the primary amenorrhea raised the suspicion of Turner syndrome or pseudohypoparathyroidism, excluded by genetic tests (karyotype 45, XX), normal phospho-calcic profile but without the posibility for GNAS1 testing. Subsequent investigations revealed an elevated TSH (7.1 μUI/ml, N: 0.4-4) with normal fT4 (1.44 ng/dl,N:0.89–1.76), FSH and LH at the upper limit (16 mIU/ml, respectively 26 mIU/ml) and the pelvic ultrasonography revealed 3–5 bilateral follicular cysts. Treatment with progesterone and 50 μg of levothyroxine was initiated, but despite treatment TSH remained unsupressed with high fT4. Five years later, after therapy had been discontinued for 3 months, she was admitted for reevaluation: tahycardia (100/min), persistent high TSH (7.88 μUI/ml) and fT4 (2.13 ng/dl) and low IGF1 (101 ng/ml, N:116-358). The rest of the hormonal profile including FSH, LH, estradiol, ACTH, cortisol, PRL were normal. The magnetic resonance imaging revealed a 11/10 mm adenoma witch raised the suspicion of a TSHoma or an incidental macroadenoma. Sex-hormone binding globulin, feritin and thyroglobulin were normal and the ultrasonography showed no goiter. On the TRH stimulation test, the brisk response of TSH (from 6.59 μUI/ml to 37.1 μUI/ml at 20 min) was suggestive for RTH. In January 2018, the patient underwent transsphenoidal pituitary adenomectomy and after removal of the tumor TSH value suddenly decreased to 0.2 μUI/ml.

Conclusions

This case highlights the difficulties in distinguishing the cause of inappropriate TSH secretion when a pituitary adenoma coexists. None of the investigations are entirely pathognomonic but a combination of tests can be suggestive of either RTH or TSHoma. In our case, although biological examination strongly suggested that this patient was suffering from RTH (normal SHBG and feritin, brisk response to TRH), the decrease in TSH value after surgery was suggestive for TSHoma. This case, along with previous reports and animals models, suggest that RTH may lead to the development of TSH-omas.

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P1001

Thyrotoxic hepatitis

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Introduction

Liver abnormalities are rarely observed in thyrotoxicosis. Diagnosis should be considered only after outruling other possibilities of hepathic pathology, especially autoimmune disaese. We report the case of a 6-year-old girl with Graves' disease who presented a liver dysfuntion.

Case report:

A 6-year-old girl with a history of Graves' disease diagnosed and treated 15 days before, was admitted for jaundice and pruritus. The interrogation finds the notion of dark urine and partially discolored stool. On physical examination, there was significant jaundice and an hepatomegaly. Laboratory exploration showed an elevated serum level of Aspartate aminotransferase at 53 IU/l, alanine aminotransferase at 68 IU/l, gamma-glutamyltransferase at 16 IU/l, alkaline phosphatase at 959 IU/l and total bilirubinemia at 48 mmol/l. Abdominal ultrasound revealed hepatomegaly with a hetero-micronodular appearance. Cholangi-MRI was normal. After excluding other etiologies for her liver injury (Obstacles to the bile ducts, viral or autoimmune hepatitis and sclerosing cholangitis) she was treated with antithyroid medications (thiamazole (thyrosol®)).The thyroid status was corrected and normalization of liver tests was observed after one month. The diagnosis of "thyrotoxic hepatitis" has been retained.

Conclusion

Hépatic manifestations of hyperthyroidism are both polymorphic and non-specific. It is essential to know how to interpret the liver manifestations that occur during the follow-up of hyperthyroidism. Although the mechanism is not completely understood, antithyroid drugs are crucial in this life-threatening hepatitis.

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P1002

Digestive system diseases associated with Turner's syndrome in 3 pediatric cases

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Objective
Considering that the patients with Turner syndrome (TS) have a high prevalence of autoimmune disease, an early investigation for digestive system diseases should be carried out in those with TS.
Case 1
A 13-year-old girl, followed for Turner's syndrome with characteristic facial dysmorphia, developed glaring diarrhea. Colon and endoscopic endoscopic examinations have led to ulcerative colitis. It was put pentasa with a favorable evolution. With a pubertal delay at the age of 15, thyroid assessment was performed concluding hypothyroidism secondary to Graves' disease. Replacement therapy with thyroid hormones has been prescribed.
Observation 2
An 11-year-old girl without dysmorphia is followed for celiac disease. The evolution under a well-monitored gluten-free diet was marked by the persistence of a weight-loss delay at −3 DS. The search for other associated pathologies has been carried out. The blood karyotype concluded that mosaic Turner syndrome was present and the patient was put on growth hormone therapy.
Observation 3
A 10 years old girl was consulted for short stature. She had also a minor dysmorphic syndrome. Hormonal investigations revealed hypergonadotropic hypogonadism. Pelvic ultrasonography showed a hypoplastic Uterus without visualization of the ovaries. Cytogenetic analysis of peripheral blood revealed a karyotype with 45 chromosomes with one X chromosome missing (45, X). Laboratory investigations revealed normal hematological and biochemical parameters except AST (107 UI/l > 45 ui/l), ALT (87 UI/l > 45 ui/l) and ALP (819 ui/l > 200 ui/l). Hepatotoxic medications and alcohol was ruled out. Abdominal ultrasonography was normal. Serology Hepatitis B and C was negative. Immunological survey showed a Anti-mitochondrial antibodies, Anti-smooth muscle antibody and Anti-LKM1 antibody were negative. But she had a positive Anti-TPO antibody with normal thyroid function tests.
Conclusion
Continuous long-term follow-up is required in patients with Tuner's disease in order to detect early the associated diseases and to prescribe appropriate treatment.

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P1003

Subacute thyroiditis in a patient with Epstein-Barr virus (EBV) meningitis

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Introduction
Viral infections have been implicated as a possible predisposing factor in the pathogenesis of subacute thyroiditis (ST). The seasonal distribution and the common clinical presentation of ST following upper respiratory track infections suggest a possible causative association. Direct serological or thyroid tissue evidence of viral infection during ST is however limited to a few case reports.
Case presentation
We present the case of a 59-year-old woman with ST 2 weeks following acute viral meningitis due to Epstein-Barr virus infection. Two weeks prior to admission, the patient developed malaise, myalgia, sore throat and mild fever. One week prior to admission she deteriorated and complained of headache, neck pain and fever up to 38.5°C. On examination there was neck stiffness and marked tenderness on palpation of the thyroid gland. Cerebrospinal fluid analysis was consistent with lymphocytic meningitis. Biochemical tests revealed elevated liver enzymes, hyperthyroxinemia (FT4 4.86 ng/dl, 0.6–1.37) with suppressed TSH and negative thyroid autoantibodies. Thyroid scintigraphy with 99mTc showed reduced uptake, consistent with thyroiditis. Serological tests were indicative of acute Epstein-Barr virus infection (positive VCA IgM and IgG antibodies). CSF culture was negative for common bacteria and PCR testing failed to detect CMV,HSV-1,HSV-2,VZV,HHV-6, enterovirus or parechovirus DNA. A month later, the patient developed hypothyroidism and was started on thyroxine replacement.
Conclusion
Only two cases of EBV associated thyroiditis have been reported so far, based on a positive titer of anti-EBV Abs or the detection of EBV DNA by PCR. We present the case of a 59-year-old woman with concomitant viral meningitis and ST and serological tests indicating acute Epstein-Barr virus infection.

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P1004

Right heart failure in patient with resistant thyrotoxicosis due to Graves' disease

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Introduction
Resistant thyrotoxicosis is condition in which patients fail to respond to maximal doses of antithyroid drugs. Definitive treatment is radioactive ablation and operative treatment. However, achievement of euthyroid status before definitive treatment is important in patients with underlying cardiovascular disorder in whom thyroid crises can be detrimental.
Case report
We describe a case of resistant thyrotoxicosis and right heart failure. A 55-year-old lady presented to our emergency center with complaints of chest pain, shortness of breath and distended stomach. On examination, she had blood pressure 140/80 mmHg, heart rate 40 bpm, jugular venous distension, pretibial edema, pansystolic murmur in the left paratsternal region and diffuse goitre. The abdomen was distended and the liver was palpable 2 cm below the right costal margin. The patient was diagnosed with Graves' disease 15 days previously in another institution and had already started taking high doses of methimazole (60 mg) and propranolol (60 mg). Blood analysis confirmed a severe hyperthyroidism with a thyroid-stimulating hormone (TSH) <0.004 uIU/ml and elevated fT4–4.03 ngl/dl (N 0.90–1.80), fT3–9.94 pg/ml (N1.80–4.20) and normocytic anaemia. Electrocardiogram showed bradicardic (40/min) sinus rhytam. Transthoracic echocardiography revealed a dilated right ventricle (52 mm) with a normal function and dimensions of left chambers. A severe tricuspid valve insufficiency was detected and estimated pulmonary artery systolic pressure was 60 mm Hg. The vena cava inferior was dilated and non-collapsing (24 mm). There was a mild mitral regurgitation grade III-IV. The methimazole was discontinued and treatment with maximum doses propylthiouracil (PTU) (300 mg three times a day), spironolacton and furosemid were initiated. The dose of propranolol was reduced (10 mg two times a day). After 2 weeks, fT4 and Ft3 were still significantly elevated and prednisolone (40 mg) was given in addition to the antithyroid drug. Four months later the patient clinically improved, but biochemical hyperthyroidism was still present. Definitive operative treatment was scheduled and in order to reduce the risk of precipitating thyroid crises the patient was given potassium iodide (150 mcg) in the next two weeks. Biochemical euthyroid state ensued and patient underwent total thyroidectomy. Thereafter tyroxine replacement therapy was started and pulmonary hypertension, atrial fibrillation and anemia resolved.
Conclusion
Addjunctive drugs like prednisolone and potasium iodide play an important role in preparing patients with resistent thyreotoxisocis for more definitive treatment.

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P1005

Pharmacologic interference as a contributory factor for spuriously elevated TSH levels

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Introduction
TRH, thyroid hormones, dopamine, somatostatin and glucocorticoids have a recognized influence on TSH secretion. On the other hand, serotoninergic, histaminergic, catecholaminergic, opioidergic and GABAergic systems establish connections with hypophysiotropic neurons involved in TSH regulation; their relative contribution to TSH secretion is unknown. Still, there are a few reports of H1 receptor antagonists impact on TSH levels.

Case report
Thirty-years-old woman with autoimmune hypothyroidism. She had been pregnant the previous year; two months after delivery she remained on euthyroidism on 112 mcg levothyroxine [TSH-1.07 μUI/ml; FT4-1.11 ng/dl]. Nine months after delivery she repeated laboratorial evaluation [TSH-16.3 μUI/ml); FT4-1.04 ng/dl] and her general practitioner increased levothyroxine dose to 137 mcg. However, two months later her TSH was still high [TSH-14.62 μUI/ml; FT4-0.91 ng/dl] and levothyroxine dose was further increased (retrospectively, she had been taking metoclopramide/betahistine on a regular basis for the previous 2 weeks). When she presented to endocrinology appointment, her pharmacologic habits included 150 mcg levothyroxine, COCP and dimenhydrinate (prescribed 3 weeks earlier for vertiginous syndrome). On that occasion, she disclaimed intermittent compliance with levothyroxine therapy. Her laboratorial re-evaluation revealed a TSH of 159.43 μUI/ml and FT4 of 1.04 ng/dl. She was summoned to repeat analysis and advised to withhold dimenhydrinate. She denied exposure to other medicines, St.John's wort, iodine supplements, iodinated contrast or amphetamines, but admitted sporadic levothyroxine omission. The following blood sample was collected one week after the former and over 24 hours off dimenhydrinate: TSH-31.86 μUI/ml; FT4-1.38 ng/dl. The laboratory was requested to exclude macro-thyrotropin: serial dilutions revealed a linear recovery. The sample was also analysed by a different method/laboratory: TSH-38.46 μUI/ml; FT4-1.45 ng/dl; rheumatoid factor assay was negative. Five weeks after dimenhydrinate withdrawal and reinforcement of the importance of medication adherence, she presented a TSH of 3.84 μUI/ml and FT4 of 1.79 ng/dl.
Discussion
A normal FT4 with a very high TSH level on a patient with a personal history of hypothyroidism might be ascribable to intermittent compliance, iatrogenic or analytical interference factors. It is important to clarify pharmacologic habits, namely exposure to dopamine antagonists, amphetamines and drugs that impair levothyroxine absorption. Likewise, methodologic interference factors such as macro-thyrotropin, rheumatoid factor and heterophile antibodies should also be regarded. Considering dimenhydrinate actions and temporal coincidence between drug exposure/withdrawal and TSH levels increase/normalization, this H1 receptor antagonist might be an important interference cofactor in the reported case.

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Developmental Endocrinology

P1006

Subacute thyroiditis with coexisting papillary carcinoma – A case report

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Introduction
Subacute thyroiditis-SAT is an acute inflammatory disease of thyroid. It is presumed to be caused by viral infection or a postviral inflammatory process. Whatever factors initiate subacute thyroiditis, the resulting thyroid inflammation damages thyroid follicles and activates proteolysis of the thyroglobulin stored within the follicles. Papillary thyroid carcinoma typically presents as a thyroid nodule. Thyroid nodules come to clinical attention when noted by the patient; during routine physical examination; or when incidentally noted during a radiologic procedure. The diagnosis of thyroid cancer is usually made by fine-needle aspiration (FNA) biopsy. SAT associated with papillary thyroid carcinoma is very rare. Only few case reports of SAT associated with papillary thyroid carcinoma have been reported in the literature.
Case report
A 49-year-old woman was admitted to hospital. She complained of fever, fatigue, malaise, anorexia, and myalgia during the last month. She had a mild pain on both side of the neck that radiated to the jaw. Physical examination revealed diffuse enlargement and mild tenderness of the thyroid gland. There were no palpable cervical lymph nodes. The rest of the exams were normal. On thyroid US, the right lobe was diffusely hypoechogenic with low flow. A hyperechogenic nodule (2.32–1.73 cm) was found in the left lobe. On laboratory investigation: TSH was 0.01 μIU/l (normal range: 0.27–4.2 μIU/l), FT4 was 23.29 pmol/l (normal range: 12–22 pmol/l), erythrocyte sedimentation rate (ESR) was 45 mm/h (normal range: 0–20 mm/h), and C-reactive protein (CRP) was 78.38 mg/l (normal range: 0.0–5.0 mg/l). A Tc-99 imaging study was done, showing low uptake in both sides of thyroid gland. FNA of the thyroid nodule on the left lobe was performed, revealing a high suspicious for malignancy (Bethesda class V). We started oral Ibuprofene 400 mg bid, and the anterior neck pain and tenderness improved within several days. Total thyroidectomy was performed and the nodule was confirmed to be papillary carcinoma, while the rest of the tissue showed granulomatous thyroiditis.
Conclusion
The ultrasound features of the nodule in our patient were not suspicious for malignancy. Despite this we performed the FNA biopsy, which revealed a Bethesda class V, confirmed by postsurgical biopsy as papillary thyroid carcinoma. Therefore, when SAT is clinically suspected, thyroid US is a useful tool for diagnosing this disorder and it may help identify a hidden thyroid malignancy.

Keywords: Subacute thyroiditis, Papillary thyroid carcinoma.
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Endocrine Disruptors

P1007

Association of Pro-inflammatory cytokines and Benign Thyroid nodules: A prospective case-control study

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Introduction
Nodular thyroid disease (NTD) is one of the commonest endocrine disease with incidence ranging from 5–30% in various populations Worldwide. They often require surgery for indications such as pressure symptoms or size related reasons. The natural history and etiopathogenesis are largely unclear except in few endemic regions. Immunomodulatory role has often been implicated in their pathogenesis. In this context, we set out study the association between Pro-inflammatory cytokines and NTD.
Material and methods
This prospective case-control study was conducted on surgically managed NTD patients. Institutional ethical committee approval was obtained. Diagnosis of NTD was based on thyroid function tests, imaging, fine needle aspiration cytology and histopathology. Exclusion criteria were subjects any systemic or chronic inflammatory disease or any medication which interferes with the normal function of the hypothalamic-pituitary-gonadal axis. Serum samples were collected from 100 HT subjects and 98 age matched healthy controls. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF-α) and high sensitive C reactive protein (hsCRP), Leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.
Results
The mean hSCRP level in NTD and controls were 11.7 ± 1.8 mg/mL and 6.2 ± 1.3 mg/mL respectively. The mean TNF-α level, IL-6 level and Leptin levels were 198.4 ± 18 pg/mL, 15.3 ± 3.2 pg/mL and 2.9 ± 1.8 ng/mL respectively. Serum leptin level in controls was 3.8 ± 2.1 ng/mL. There was statistically significant difference of all the pro-inflammatory cytokines compared to controls (P value < 0.05).
Conclusions
This study shows raised titers of pro-inflammatory markers – IL-6, TNF-α and hsCRP correlated with NTD suggesting a contributory role. Leptin appears to have no definitive correlation with NTD. But, the exact immuno-modulatory role and pathogenetic mechanism needs active research.

Keywords: Thyroid nodules, Tumour necrosis factor, Interleukin-6, Goiter, Auto-immunity, Leptin
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P1008

A validated LC-Q-TOF-MS method for quantitative analysis of thyroxine and metabolites in placenta

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Thyroid hormones (TH) of maternal origin are critical for the proper fetal development, especially during early pregnancy. Even minor changes in maternal TH circulation can lead to various adverse outcomes. Recent studies found that the metabolites of thyroxine (T_4) also play an important physiological role. For example, 3,5-diiodo-L-thyronine (T_2) and 3,3′-diiodo-L-thyronine (rT_2) can suppress the thyroid stimulating hormone (TSH) level and increase the resting metabolic rate. 3-iodothyronamine (T_1AM) administration in mice leads to a hypometabolic state. These metabolites may have influences on the fetus. Having the capacity to make a comprehensive analysis of T_4 and the metabolites in placenta provides a diagnostic tool for the placental TH homeostasis. Routine TH assessment has long been achieved by measuring T_4, triiodo-L-thyronine (T_3), and TSH in blood using immunoassay (IA) method, which is of high sensitivity, but is prone to nonspecific interferences. Methods based on liquid chromatography-mass spectrometry (LC-MS) and tandem mass spectrometry (LC-MS/MS) showed better accuracy and reliability. In this study, we report a method for the determination of T_4, T_3, 3,3′,5′-triiodo-L-thyronine (rT_3), T_2, rT_2, 3-iodo-L-thyronine (T_1), and T_1AM in the placenta. The method was optimized using isotope (^{13}C-T_4, ^{13}C-T_3, ^{13}C-rT_3, ^{13}C-T_2) dilution methodology and determined by liquid chromatography quadrupole time-of-flight mass spectrometry (LC-Q-TOF-MS). The calibration ranges from 0.5 to 150 ng/ml with R^2 values > 0.99. The method detection limits (MDLs) and the method quantification limits (MQLs) were 0.01–0.2 ng/g and 0.04–0.7 ng/g, respectively. The spike-recoveries for THs (except for T_1 and T_1AM) were between 81.0% and 112%, with a coefficient of variation (CV) of 0.5–6.2%. The intra-day CVs and inter-day CVs were 0.5% – 10.3% and 1.19% – 8.88%, respectively. The method was adopted for TH measurement in human and mouse placenta. The concentrations of T_4, T_3, rT_3, and T_2 were 22.9–35.0 ng/g, 0.32–0.46 ng/g, 2.86–3.69 ng/g, and 0.16–0.26 ng/g in human placenta, and 2.05–3.51 ng/g, 0.37–0.62 ng/g, 0.96–1.3 ng/g, and 0.07–0.13 ng/g in mouse placenta, respectively. The presence of T_2 was tracked in placenta tissue for the first time, indicating improved selectivity and sensitivity of our method. The validated method allows comprehensive evaluation of total T_4 and metabolites in the placenta.

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Endocrine Tumours and Neoplasia

P1009

Bethesda System for Reporting Thyroid Cytopathology (BSRTC): Category III and IV Frequency and Risk of Malignancyin the Era of Molecular Testing and after the Reclassification of Non Invasive Follicular Thyroid Neoplasms with Papillary-Like Nuclear Features (NIFTPs)

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Background

The BSRTC aimed to standardize thyroid cytopathology reporting while enabling stratification of risk of malignancy (ROM) in thyroid nodules. Observational studies have demonstrated varying ROM for the Bethesda III and IV categories, further affected by the recent exemption of NIFTP. Finally, molecular testing is becoming a reasonable alternative for evaluating ROM in categories III and IV.

Objective

To retrospectively establish the use of Bethesda categories III and IV in specimens obtained from FNAs at Tel Aviv Sourasky Medical Center over a 3 year period, to assess the ROM in these categories in the era of molecular testing and NIFTP, and to examine clinical correlates that might affect the ROM.

Methods

Aspirated thyroid nodules between January 2013 and December 2015 were reviewed. Files of patients with nodules classified as category III and IV were searched for downstream surgical procedures, repeat FNA and/or Afirma® gene classifier testing, in order to determine their outcome. Confirmed NIFTPS were considered benign lesions. Sonographic characteristics and potential clinical risk factors for malignancy were evaluated for category III and IV nodules.

Results

Of 3701 nodules aspirated on 2674 subjects (80% women/20% men, age 56.7 ± 15.5 y), 6.5% were Bethesda-I, 72.8% Bethesda-II, 7.7% Bethesda-III, 3.6% Bethesda-IV, 2.3% Bethesda-V, and 7.2% Bethesda-VI. A diagnostic outcome was available for 128 of the 284 category III nodules: 18 (14.0%) were malignant (16.4% if NIFTP included), and 109 (86.0%) were benign. The outcome was known for 60 of the 132 category IV nodules, 17 (28.3%) were malignant (31.7% if NIFTP included), and 43 (71.7%) were benign. Male gender and smoking were significant and independent risk factors for malignancy in Bethesda III, but not in Bethesda IV nodules. Age, country of birth, family history of thyroid cancer, nodule size, and a cumulative score of 5 suspicious sonographic characteristics were not predictive of malignancy in either category.

Conclusion

The distribution of the various Bethesda categories in our study, and specifically categories III and IV, was consistent with previous published reports. The ROM for Bethesda III and IV nodules was also in line with recent reports. Exclusion of NIFTP from malignancy did not significantly affect these figures. Although we identified several factors that increased the ROM, their predictive value was not powerful enough to be acted upon. Better molecular tools are needed to further reduce the number of unnecessary surgeries in this age of epidemic of incidentally discovered thyroid nodules.

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P1010

Thresholds of basal and calcium stimulated calcitonin for diagnosis of medullary thyroid carcinoma

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Introduction

The current revised medullary thyroid carcinoma (MTC) guidelines don't specify reference ranges of basal (bCT) or stimulated serum calcitonin (sCT) levels for the diagnosis of MTC. These are important for early diagnosis and correct management.

Objective

We aimed to set gender specific thresholds for bCT and sCT for MTC diagnosis.

Patients and methods

CT samples during calcium-stimulation test (25 mg/kgBW adapted on ideal body mass index) before and at 2, 5 and 10 minutes after administration were measured before thyroidectomy in 31 patients with thyroid nodules: 21 Females(F) – 10 Males(M), aged 47 y (23–67). bCT and sCT were compared with histological results. CT was measured by immunochemiluminescence.

Results

The test was well-tolerated, with minimum side-effects. For 8 patients with bCT < 10 pg/ml (8F), the mean peak sCT was 106.6 pg/ml ± 197.12 (range:1.02–576). We identified 2 MTC, 1 papillary thyroid carcinoma (PTC) and 5-benign lesions. For 23 patients with bCT > 10 pg/ml (13F–10M), the mean bCT and peak sCT were:28.49 ± 26.9 pg/ml (range:11.57–104.4), respectively 356.35 ± 206.07 pg/ml (range:98.1–724.6) in F, and 26.99 ± 17.4 pg/ml (range:10.86–67.2), respectively 465.71 ± 440.43 pg/ml (range:73.07–1571) in M. Histologically, we identified MTC in 6F and 1M, associated with C-cell hyperplasia (CCH) in 2 and with PTC in 3 cases. For the remaining cases, CCH in 1F and 2M; PTC in 4F and 3M; 1 follicular thyroid carcinoma in 1M and benign lesions in 2F and 3M. The best CT thresholds to discriminate normal cases from patients with either MTC or CCH were: 19.85 pg/ml for bCT (sensitivity – 66.7%; specificity-89.5%), AUC 0.77 (CI:0.60–0.95), $P = 0.01$, and 244.65 pg/ml for sCT (sensitivity – 75%; specificity – 63.2%), AUC 0.73 (CI:0.55–0.91), $P = 0.03$. For F, the best thresholds to discriminate normal cases from patients with either

MTC or CCH were: 13.15 pg/ml for bCT (sensitivity – 77.8%; specificity – 75%), AUC 0.82 (CI:0.64–1), $P=0.01$, and 208.2 pg/ml for sCT (sensitivity – 77.8%; specificity – 75%), AUC 0.78 (CI:0.58–0.98), $P=0.02$. Genetic results are awaited and other histopathologic evaluations are scheduled.
Conclusions
Our study found bCT and sCT cut-offs for discriminating MTC or CCH from normal subjects. The calcium gluconate test is well tolerated and safe to use. Larger studies are needed for accurate cut-offs that may improve diagnosis not only of MTC in early stages, but, interestingly enough, for PTC.

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Nuclear Receptors and Signal Transduction

P1011

Are benign adenoma and papillary thyroid carcinoma related? A linkage study from BRAF and NIS gene mutation point of view

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Introduction
The adenoma – carcinoma sequence in thyroid nodules is a enigmatic phenomenon. There are conflicting reports on development of papillary cancer from benign adenomas. Genomics is the only definitive modality to resolve this hypothesis. Adenomas and papillary carcinomas tend to have mutations in Sodium Iodide symporter gene (NIS) and highly specific BRAF gene respectively. In this context, we set out study the prevalence of these somatic mutations in surgical tissue samples.
Material and methods
This prospective study was conducted on surgically managed thyroid nodule patients. Institutional ethical committee approval was obtained. Diagnosis was based on biochemical confirmation, imaging, fine needle aspiration cytology and later confirmed by histopathology. All cases underwent total thyroidectomy along with additional neck dissection in cancer cases. We selected 25 benign thyroid adenomas (BTA) and 20 papillary thyroid carcinoma (PTC) cases. Tumour tissue samples were taken from *ex-vivo* specimen within operation theatre. After appropriate processing of samples, DNA extraction, cDNA preparation, PCR amplification, application of 6 sets of Primers were performed as part of mutational analysis of NIS and BRAF genes.
Results
Heterozygous mutations in NIS were found in 11/25 (44%) of BTA and 5/20 (25%) of PTC cases. A recessive heterozygous mutation in BRAF was found in PTC cases (9/20) only. No BRAF mutations were noted in BTA.
Conclusions
NIS mutations were prevalent in both benign and malignant thyroid nodules giving some evidence for linkage between them. Though not robust, we opine that there is possibility of adenoma- carcinoma sequence in thyroid nodules. BRAF mutations appear to be specific to PTC. We need larger, robust and consistent studies to justify this observation in future.
Keywords: Papillary thyroid cancer, BRAF gene, NIS gene, Thyroidectomy, Goiter

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Paediatric Endocrinology

P1012

Characteristics of thyroid dysfunction in children with turner syndrome

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Objectives
To evaluate the prevalence and characteristics of thyroid diseases in children with Turner syndrome (TS).
Methods
This is a retrospective study, analyzing clinical data from medical records of 19 patients with TS from 3 to 17 years (average age 12.02 ± 4.0 years), who were regularly followed-up in the University hospital (Minsk). Depending on the karyotype, 3 groups of patients were identified: the first group with karyotype 45, X ($n=8$), the second group with mosaic variant 45,X/46,XX ($n=3$), the third group with structural anomalies of X chromosome ($n=8$). All patients were evaluated for thyroid function (TSH and free T4) and autoimmunity (anti-TPO antibodies (ATPO)), thyroid ultrasound examination was performed. The results were processed using SPSS.22.
Results
TS was diagnosed in patients with characteristic phenotypic signs according to the results of karyotyping at the age of 3.78 ± 3.48 years. 42% of girls ($n=8$) had normal thyroid function with TSH level of 2.61 ± 0.76 μIU/ml, 58% ($n=11$) had subclinical hypothyroidism (TSH – 7.5 ± 1.78 μIU/ml and normal level of fT4). Subclinical thyroid dysfunction was revealed in 66.7% girls with mosaic karyotype ($n=2$, TSH – 6.36 ± 0.79 μIU/ml), in 62,5% girls with monosomy X ($n=5$; TSH – 7.45 ± 1.92 μIU/ml), less often (50%, $n=4$) in girls with a mutation of the X chromosome (TSH 8.14 ± 2 μIU/ml). The prevalence of ATPO positivity was found to be 31.6% ($n=6$). Most of ATPO positive patients were girls with structural anomalies of the X chromosome (50% of patients, $n=4$). All patients with thyroid dysfunction are treated with levothyroxine, the average daily dose is 1.07 ± 0.53 μ/kg. There were no changes in the structure and size of the thyroid gland in 68.4% of girls ($n=13$) according to ultrasound. Sings of autoimmune thyroid disease (AITD) were found in 26.3% ($n=5$), nodal pathology – in 5.3% ($n=1$). Ultrasound symptoms of AITD were more common in girls with structural anomalies of the X chromosome (37.5%, $n=3$).
Conclusions
Our data showed high frequency of subclinical hypothyroidism in girls with TS. Thyroid autoimmunity in TS patients is more often detected in the presence of structural anomalies of the X chromosome.

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Thyroid (non-cancer)

P1013

Assessment of radioiodine treatment for hyperthyroidism

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Introduction
Hyperthyroidism owing to Graves' disease or toxic nodular goiter is a common condition seen in clinical practice. The available modes of therapy are antithyroid drugs, surgery and radioiodine (RAI) therapy. Radioiodine is an effective, safe and relatively inexpensive form of therapy in patients suffering from hyperthyroidism. The aim of our study is to assess the effectiveness of radioactive iodine (RAI) treatment in patients with hyperthyroidism.
Methods
We retrospectively analyzed 70 patients suffering from hyperthyroidism and receiving RAI treatment. They were diagnosed as having hyperthyroidism based on clinical symptoms, elevated thyroid hormone levels and suppressed thyroid-stimulating hormone levels.
Results
The mean age of the study population was 38.33 ± 13.11 years. Forty-seven patients were female (67.1%) and 23 were male (32.9%). Sixty-five percent had Graves 'disease, 32% had toxic multinodular goiter and 3% had toxic single nodule. Sixty-five percent had been pre-treated with anti-thyroid medications. The mean duration of follow-up was 25.14 ± 14.25 months. The average dose of I131 used for therapy in our patients was 14.15 ± 0.34 mCi. Mean serum levels of free thyroid hormones were significantly lower in patients with toxic multinodular goiter compared to patients with Graves' disease (38.2 vs 58.6 pmol/l, $P=0.04$). Mean thyroid volume, as assessed by ultrasonography, was larger in patients with toxic multinodular goiter than in patients with Graves' disease (61.2 vs 24.2 ml, $P<0.01$). Patients with toxic multinodular goiter received a significantly higher dose of iodine than patients with Graves' disease (14.2 vs 12.3 mCi, $P<0.01$). The incidence of hypothyroidism was 52% at 6 months and 61% at one year. The response rate was significantly higher in the group without pre-treatment with anti-thyroid medications.The levels of serum thyroid hormone at presentation were correlated with the development of hypothyroidism after RAI treatment.
Conclusion
Radioactive iodine treatment is an effective modality for definitive treatment of hyperthyroidism. Response rate was not related to gender, etiology or RAI dosage. Pre-treatment with anti-thyroid medication reduces the response rate.

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P1014

Dyslipidemia in subclinical hypothyroidism: a case–control study

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Background
Subclinical hypothyroidism (SCH) is a common condition affecting 7.5–8.5% of women and 2.8–4.4% of men. Overt hypothyroidism is characterized by dyslipidemia, however the controversy persists regarding the lipids level in subclinical hypothyroidism (SCH) and its clinical significance. Recent evidence also shows that T4 replacement therapy may improve lipid profile.
Aim
The aim of this study is to assess the prevalence of dyslipidemia in subclinical hypothyroidism, to the best of our knowledge; this is the first study to assess dyslipidemia among patients with subclinical hypothyroidism in Duhok, Iraq.
Methods
This is a case-control study, consisted of a total 120 individuals, the case group composed of 60 patients diagnosed with subclinical hypothyroidism, while control group composed of 60 healthy individuals (matched for age and gender). The study conducted at the endocrine clinic at Azadi Teaching Hospital in Duhok Governorate, Kurdistan Region, Iraq from from 1st June 2016 to 1st June 2017.
Results
Dyslipidemia was much more prevalent in patients with subclinical hypothyroidism in comparison to control group (P value <0.001). In further analysis of dyslipidemia total cholesterol and triglyceride levels were statistically higher among cases in comparison to controls (P value <0.001) for both. LDL level was higher among cases in comparison to controls; however it didn't reach statistical significance (P value of 0.087). While there was significant difference regarding HDL level among female gender cases and Controls (P value of 0.003), there was no significant difference regarding difference in HDL level among male gender cases and Controls (P value is 0.653).
Conclusion and recommendations
SCH is considered atherogenic condition as it increases dyslipidemia and it increases overall cardiovascular risk. It's reasonable to assess lipid profile and CVS risk in these patients and to treat with levothyroxine when it's clinically applicable.

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P1015

An eleven–year–old girl presenting with Graves' ophtalmopathy

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Introduction
Graves' ophthalmopathy (GO) is an autoimmune disorder affecting the retro-orbital tissues. It represents the main extra- thyroidal expression of Graves' disease (GD). In children, GO is less common and less severe than in adults. Herein we report a case of GO in a child.
Case report
An 11-year-old girl with family history of autoimmune thyroid disease was referred to our department for evaluation of suspected hyperthyroidism. She presented with heat intolerance, diaphoresis, palpitations, mood disturbances, tearing, photophobia, gritty eyes as well as a history of weight loss over the past few months. On physical examination, she had a body weight of 40 kg, a BMI of 16.65 kg/m^2. The pulse rate was 110 beats per minute (bpm). A diffuse goiter and a mild bilateral exophthalmos were also found. At the admission, laboratory tests revealed decreased TSH (<0.005 μIU/ml) and increased free T4 of 26.9 pmol/l. TSH receptors antibodies were positive. Doppler Ultrasonography revealed enlarged thyroid without focal lesions, with increased vascular flow in both lobes. The diagnosis of Graves' disease was established. Treatment with Methimazole (15 mg) and propranolol (20 mg*3) was then initiated. Lubricating eye drops were prescribed for the ocular symptoms. Thyroid hormone levels normalized after 2 weeks and the girl was discharged from the hospital in good condition.
Conclusion
Although rare in childhood, GD remains the most prevalent cause of hyperthyroidism. Its ocular manifestations are much milder than in adult GO and their management requires, in the majority of cases, only a local treatment. A regular follow up is always needed.

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P1016

Choroidal thickness changes in Graves' ophthalmopathy

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Introduction
Graves' ophthalmopathy (GO) may develop nearly 25–50% in Graves' Disease (GD). Clinical manifestations of GO are caused by the over compression of orbital tissues within the restricted orbital bone cavity. Impaired ocular blood flow may disrupt the retinal microstructure and functions. Early recognition of retinal and choroidal changes may alert the physicians for preventing ocular complications of GO. In this study we aimed to investigate the macular and choroidal thickness changes in GO compared with healthy subjects.
Materials and methods
The study group comprised 50 adult patients with previously diagnosed Graves' Disease with ophthalmopathy who were on anti thyroid treatment, compared with controls. For the assessment of GO activity, VISA (vision, inflammation, strabismus, and appearance) inflammatory score was used. When euthryoidism was achieved without side effects, the patients were referred to the ophthalmology clinic for Spectral-domain optical coherence tomography (SD-OCT) evaluation. SD-OCT is a non-invasive method that is used for quantitive assessment of retinal morphology and choroidal thickness.
Results
Subfoveal, mean and temporal choroidal thicknesses were increased significantly in study group according to the controls. But nasal, peripapillary and choroidal thickness minimal increased in study group and there was no statistical difference. None of our patients had severe GO, and the mean intraocular pressure (IOP) was within the normal limits. However, the mean choroidal thickness was elevated.
Conclusions
We think that this elevation is because of the retroorbital inflammation even in this non-severe GO group. We also suggest that choroidal thickness might be affected from the venous obstruction and congestion in patients with GO. The elevation of the choroidal thickness might be an early sign of venous congestion that occurs before the elevation of IOP (Table 1).

Table 1 Choroidal thickness differences between groups.

	Study group n = 50	Control group n = 50	P value*
Subfoveal	304.22 ± 36.09	275.54 ± 34.20	$P<0.001$
Temporal, 500 μm	311.06 ± 38.18	274.22 ± 34.92	$P<0.001$
Temporal, 1000 μm	309.68 ± 36.83	272.98 ± 33.24	$P<0.001$
Temporal, 1500 μm	302.00 ± 32.44	267.64 ± 31.77	$P<0.001$
Nasal, 500 μm	294.10 ± 34.74	270.76 ± 34.66	$P=0.001$
Nasal, 1000 μm	274.50 ± 38.92	263.50 ± 34.06	$P=0.13$
Nasal, 1500 μm	256.04 ± 43.27	253.10 ± 34.73	$P=0.70$
Mean	293.08 ± 34.81	268.24 ± 33.11	$P<0.001$

*Student T test.

This study has been presented as a poster (P176) at the 87th Annual Meeting of the American Thyroid Association. October 18–22, 2017. Victoria, BC, Canada.

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P1017

Post-operative hypocalcaemia following open thyroidectomy for benign multinodular goiters using FOCUS harmonic scalpel versus conventional suture ligation technique for hemostasis – a prospective, single-blind, randomized controlled trial

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Background
Vessel hemostasis during thyroidectomy is the mainstay of reducing the risk of post-operative hypocalcaemia, which can be achieved by using several techniques. The aim of this study was to compare the occurrence of hypocalcaemia 24–48 hours following total thyroidectomy by using FOCUS harmonic scalpel (HS) vs the conventional suture ligation (CSL).

Patients and methods
A prospective, single-blind, randomized trial in which 76 patients with benign multinodular goiters scheduled to undergo total thyroidectomy, were randomized into two groups: to receive HS ($n=38$) or CSL (38). Patients were monitored for hypocalcaemia at 24 and 48 h post-operatively and the lengths of post-operative hospital stay. Statistical analysis to detect between-group difference was based on student's *t*-test performed using SPSS.
Results
The incidence post-operative hypocalcaemia was 15.79% and 36.84%, in HS and CSL groups, respectively ($P=0.033$). Length of hospital stay was 2.63 ± 0.85 and 1.37 ± 0.67 days, respectively ($P<0.001$), identification of parathyroid glands was significantly associated with hypocalcaemia in the CSL group ($P=0.019$) but not in the HS group ($P=0.372$).
Conclusions
FOCUS HS is a reliable and safe technique, with the potential of achieving hemostasis in total thyroidectomy for benign thyroid disease. The conventional suture ligation technique should be replaced with FOCUS HS in thyroid surgery practice.
Keywords: Conventional hemostasis, Harmonic scalpel, suture ligation, Multi-nodular goiters, thyroidectomy
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P1018

Thyroid disorders and gestational diabetes mellitus: more common than we thought

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Aim
Thyroid disorders are very common in women of reproductive age. The aim of this study was to determine the prevalence of different biological thyroid disorders during gestational diabetes mellitus (GDM).
Methods
This was a retrospective observational study carried out between March and June 2017 in the day hospital of the National Institute of Nutrition. Pregnant women referred for the management of GDM and who have no history of prior thyroid disorders were included. Five forms of thyroid disorders have been identified: Isolated hypothyroxinemia, Overt Hypothyroidism, Subclinical Hypothyroidism, Overt hyperthyroidism and Subclinical hyperthyroidism. Clinical and bio-chemical data were obtained by review of medical records.
Results
We included 100 pregnant women with a mean age of 32.4 ± 5.3 years. Of them, 4% were in the first, 35% in the second and 61% in the third trimester of pregnancy. Mean gestational age at time of screening for GDM was 22.3 ± 6 weeks. Approximately 47% of pregnant women were euthyroid, 20% were hypothyroid and 4% were hyperthyroid. Isolated hypothyroxinemia was detected at 29% of women. Hypothyroidism, defined as an elevated TSH level above the trimester-specific reference range, was associated with a decreased level of free T4 (overt hypothyroidism) in 16% and with a normal level of circulating free T4 in 4% of the population (subclinical hypothyroidism). The incidence of overt and subclinical hyperthyroidism in pregnant women was around 1% and 3%, respectively.The presence of thyroid disorders was noted in 40% of pregnant women during the first trimester, in 53% of pregnant women during the 2nd trimester and in 54% during the 3rd trimester.
Conclusion
Our results showed that thyroid disorders are common in our study population. A reassessment of the iodine status of Tunisian women is interesting to detect a possible deficit and therefore introduce targeted supplementation.
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P1019

Characteristics and outcome of patients with hyperthyroidism attending a hospital endocrine clinic- a retrospective study

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Aims
A study looking at the incidence, presentation, diagnosis, management strategies and outcomes following anti-thyroid drug treatment and radio-iodine therapy in a cohort of patients presenting with hyperthyroidism.
Methods
Retrospective longitudinal study of all patients ($n=442$) who received treatment for a new diagnosis of hyperthyroidism (Grave's disease (GD), multinodular goitre (MNG), Toxic nodule) in a secondary care outpatient setting over a 15 year period (2002-17). All patients are initially treated with thionamides for at least a 6 month period, and up to 2 years until a biochemical remission (TSH level within the normal range) is observed for at least 6 months after cessation of drug treatment. A second course of treatment is offered to patients in cases of relapse, but treatment is individualised depending on personal circumstance, aetiology and patient preference.
Results
442 patients were treated with thionamides between 2002 and 2017. Mean duration of treatment was 295 days (range min-max). The age of diagnosis ranges between 17 and 91 years (mean 52.6 ± 17.1 years) with female (74.4%) to male (25.6%) ratio of 3:1. 78.5% ($n=347$) of subjects had Graves disease, 8.4% ($n=37$) had multinodular goitre (MNG), 6.6% ($n=29$) had amiodarone induced thyrotoxicosis and $n=16$ (6%) had toxic nodule. A biochemical cure on drug treatment was achieved in 161 patients (37%), and of these 93% ($n=150$) had Graves, 4.4% (N=7) had multinodular goitre 2.5% ($n=4$) had thyroid nodule. In 122 patients who received radioiodine, 70% ($n=85$) had Graves disease, 15% ($n=18$) had multinodular goitre, 13% ($n=16$) had toxic nodule, 2% ($n=3$) were of indeterminate aetiology. In 18 patients who received a 2nd dose of radioiodine, 67% ($n=12$) had Graves disease, 11% ($n=2$) had multinodular goitre, and 22% ($n=4$) had toxic nodule. 50% ($n=61$) patients developed permanent hypothyroidism within 6 months of radioiodine therapy. Of these 65% ($n=56$) had Graves disease, 22% ($n=4$) patients had MNG and 25% ($n=1$) had toxic nodule. In 8 patients who underwent a thyroidectomy, 6 had Graves' disease and 2 had amiodarone induced thyrotoxicosis.
Conclusions
This is the first study to report characteristics of patients with hyperthyroidism in a UK population managed in the outpatient setting. Although the data may be limited by some incomplete records commonly encountered in retrospective series, we present some interesting findings showing the likely clinical response rates to various established treatment modalities used.
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P1020

How evolve antithyroperoxydase antibody in Hashimoto thyroiditis in time: Study on 450 patients: January 2018

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Aim
Most research teams analyze the evolution of patients with Hashimoto thyroiditis (HT) on syndromal basis, not on pathogenetic basis. Thus, most researchers refer to thyroid function evolution. In this study we tried to show how evolve the antithyroid antibodies. Therefore, we analyzed ATPO evolutive patterns.
Method
(1) ATPO levels were analyzed in several accreditated Bucharest laboratories. (2) Only patients with minimum 3 investigations were considered for interpretation. (3) We considered 5 ATPO evolutive patterns: (a) undulatorious; (b) decreasing; (c) increasing; (d) unmodified, (e) disappearance. (4) Unmodified pattern was considered if ATPO level did not differed by 5%. (5) Disappearance pattern was considered if ATPO decreased under the cut off level (=34 ui/ml).
Results
(A) Patients: 450; women – 421, men – 29 (6.89%). (B) The reinvestigation final time was: average: 5.37 years; median: 4.75; minimum: 2 months, maximum: 22 years. (C) ATPO level at onset (diagnostic time): average: 854 ui/ml, standard deviation: 2508. (D) The evolution patterns were: (a) undulatorious – 313 patients (69.5%); 5 without thyroid; (b) decreasing (ATPO over cut off limit) – 76 (17%); 3 no thyroid (1 – atrophy, 2 thyroidectomy/TX); (c) increasing: 36 (8%); (d) unmodified: 12 (2.67%), 2 no thyroid (1 after 131-I, 1 TX); (e) disappearance: 13 patients (2.9%), 8 no thyroid (3 atrophy, 5 TX). (E) ATPO patterns in patients (no. 68) seen after 10 years: (a) undulatorious: 51 (75%); (b) decreasing: 11 (16%) ; increasing: 1; unmodified: 1; (e) disappearance: 4 (6%). (F) There was no clear correlation with thyroid function at onset: Hypothyroidism vs euthyroidism vs hyperthyroidism: (a): 153-113-47; (b): 31-30-15; (c): 16-13-7; (d): 3-7-2; (*z* test, $P>0.005$); (e): 13-0 – significant difference.
Conclusions
(1) In most patients (c. 70%), ATPO evolve undulatorious. (2) When thyroid is missing, ATPO decreased level were registered till disappearance.
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P1021

Hyperemesis gravidarum mimicking thyroid storm- A diagnostic dilemma in early pregnancy

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Introduction
The thyrotrophic effects of human chorionic gonadotrophin (HCG) are responsible for a physiological rise in fT4 and suppression of TSH in early pregnancy. Hyperthyroidism in this period is mostly due to gestational transient thyrotoxicosis (GTT) which is frequently mild and resolves spontaneously by 18 weeks, or due to Graves' disease (GD) which would require closer monitoring through pregnancy (1). The pathophysiology of hyperemesis gravidarum is unclear, although it has been associated with higher HCG and fT4 levels. Here, a case of severe hyperemesis gravidarum (HG) presenting with features of thyroid storm is described.
Case
A 24 year-old primip with singleton pregnancy and no previous thyroid disease presented at 9 weeks gestation with a 3-week history of nausea, vomiting, anorexia, lethargy and 10% weight loss. Additional symptoms included palpitations and heat intolerance. Clinically, she was thin, dehydrated and anxious. She was afebrile, BP 110/76 mmHg with tachycardia at 150 per minute. Fine tremors were present. She had neither goitre nor other features of Graves' disease. Hyperthyroidism was confirmed biochemically – fT4 50.6 pmol/l [Reference Interval (RI): 8–21 pmol/l], fT3 14.6 pmol/l [RI 3.5–6.0 pmol/l], TSH 0.01 mIU/l [RI: 0.34–5.60 mIU/l]. LFT showed a mixed picture with bilirubin 3 times elevated and transaminases raised between 5 and 9 times. White cells count and erythrocyte sediment rates were normal. ECG showed T inversions. Burch-Wartofsky score was 50. She was supported with intravenous infusion and anti-emetic which stabilized her pulse to 120 per minute. In view overt clinical features of hyperthyroidism, carbimazole 30mg was given daily. Daily fT3 showed an improving trend and she was discharged on day 4 when fT4 31.4 pmol/l, fT3 8.6 pmol/l, TSH <0.01 mIU/l. Carbimazole was stopped 2 weeks later. Her thyroid antibodies eventually returned as negative. She delivered a healthy baby girl at term and post-partum thyroid tests were normal.
Discussion
While GTT is largely a benign condition, serious complications had been reported. Confident differentiation of GTT from GD relies on evidence of thyroid autoimmunity. Delaying definitive treatment while awaiting antibody testing results may expose the patient to adverse effects of hyperthyroidism. In cases with features of severe hyperthyroidism, a short course of ATD may be necessary to avoid further end-organ deterioration while maintaining close monitoring of thyroid levels to avoid over-treatment.
Reference
[1] Ide *et al.* Comparative frequency of four different types of pregnancy-associated thyrotoxicosis in a single thyroid centre. Thyroid Research (2017) 10:4.

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P1022

Correlation between cytologic results and thyroid autoantibodies, calcitonin, and thyroid function tests in patients with thyroid nodules

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Aim
Fine needle aspiration biopsy (FNAB) is currently a widely accepted screening procedure in diagnosis of thyroid nodules, there has been confusion related to diagnostic terminology in the assessment of samples. This confusion has been caused by multiple category names, descriptive reports without assigning to a category, and different terminologies used for surgical pathology. We aimed to evaluate correlations between US characteristics, cytologic results of FNAB, and thyroid antibodies, calcitonin, and thyroid function tests in patients presented with thyroid nodules, and to contribute in diagnosis, treatment, and patient follow-up.
Methods
A total of 1639 patients with thyroid nodules who applied to outpatient clinic of endocrinology between dates April and May 2017, had FNAB under US guideline, and their pathologic evaluation was performed according to Bethesda classification. Serological and hormonal tests were also performed for each patient.
Results
The mean age of study group was 50 (range interval = 14–90) years. The median of node-diameter1 was 17.5 (range = 1–51) mm, and median of node-diameter 2 was 12 (range = 8–33) mm. Of US characteristics, echogenicity, microcalcification, irregular borders, and solitary nodules were determined in 4.4%, 54%, 71.2%, and 86.6% of cohort respectively. Elevated anti-TPO was determined in 64.6%. Cytologic readings were reported as 15.8% nondiagnostic, 53.8% atypia of undetermined significance/follicular lesion of undetermined significance, 28.8% benign, 0.4% suspicious for follicular nodule, and 1.2% malign.
Conclusion
FNAB, high resolution US findings, and sensitive thyrotropin levels are the mainstay to determine further clinical approach in patients with thyroid nodules.

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P1023

Percutaneous ethanol injection for benign cystic and mixed thyroid nodules

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Background/aim
We aimed to determine the effect of percutaneous ethanol injection (PEI) on volume of cystic and mixt thyroid nodules, thyroid function tests (TFTs), antibody titers and cytological changes for 1 year.
Methods
Fifty-five nodules of 53 patients with cystic and mixt properties treated with PEI were included. Nodule volumes, TFTs, thyroid autoantibodies were analyzed at baseline, 6^{th} and 12^{th} months. Fine needle aspiration biopsy (FNAB) was performed to PEI applied nodules in the 12^{th} month. Thyroid nodules were grouped into three by structural properties (pure cystic, predominant cystic, predominant solid). By calculating volume reduction between initial and final volume, we defined response to PEI in three categories as complete response ($\geq$90%), partial response ($<$90% to $\geq$50), and no response ($<$%50).
Results
PEI caused a volume reduction of 80.7% at 6^{th} month and 82.1% at 12^{th}month without any serious complication. PEI was repeated 1.4 ± 0.4 times with a mean total ethanol amount of 3.6 ± 3.1 ml. Volume reduction in the pure cystic nodules at 6th and 12th months after PEI was greater than the volume reductions in predominant cystic and predominant solid nodules. We detected that smaller nodules have greater volume reductions after PEI at 12th month. During the study, patients remained euthyroid. Anti-thyroglobulin levels were decreased at 12^{th} months. None of the FNAB results was compatible with a malignant or suspicious for malignancy cytology at 12^{th}month.
Conclusion
PEI is an effective way of treatment for benign cystic and mixt thyroid nodules without any serious side effects. We can also assume that PEI is not a trigger for autoimmunity and carcinogenesis for short term.

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P1024

Post partum and non-post partum relapsing Graves' hyperthyroidism display different response to anti-thyroid drugs

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Background
Graves' disease (GD) female patients in remission after a full course of methimazole (MMI) therapy are at risk for a relapse of hyperthyroidism during the post-partum (PP) period, but whether this relapse may display any peculiarity is still unknown.
Aim
To compare GD patients undergoing a relapse of hyperthyroidism either in the PP period or not.

Subjects and methods
Fourty-three female patients of childbearing age experiencing a relapse of GD hyperthyroidism were retrospectively evaluated. In 18 of them the relapse occurred in the PP period (i.e. within 12 months after delivery, PP group); in the remaining 25 the relapse occurred elsewhere during life (NPP group).
Results
At the time of the relapse, patients in the PP and NPP group were similar in terms of: age (34.4 ± 6.0 years versus 36.9 ± 5.7 years NS), thyroid volume (17.4 ± 6.9 ml vs 17.4 ± 6.1 ml, NS), thyroid function tests (FT3 7.64 ± 4.05 pg/ml vs 8.07 ± 3.67 pg/ml, NS) TRAb titers (4.37 ± 2.95 U/l versus 7.25 ± 7.22 U/l NS) and MMI starting dose (20.3 ± 8.0 mg/day vs 20.6 ± 9.01 mg/day, NS). However, the remission rate after a 12-month of MMI course was much greater (79%) in the PP as compared with the NPP (32%) group ($P = 0.002$). Throughout the study span, a significant reduction in TRAb levels was observed in the PP ($F = 9.016$; $P = 0.001$), but not in the NPP group ($F = 2.433$; NS). At 12 months the PP group also showed significantly lower mean TRAb levels (0.6 ± 1.1 U/L vs 4.5 ± 4.7 U/l, for PP and NPP, respectively; $P = 0.029$).
Conclusions
Relapsing Graves' hyperthyroidism in the PP period is more prone to undergo a remission of hyperthyroidism after a second course of MMI. A conservative therapeutic approach seems than to be more appropriate in GD patients experiencing a relapse of hyperthyroidism in the PP period.

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P1025

Rare association of primary hyperparathyroidism and toxic multinodular goiter

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Introduction
The association of primary hyperparathyroidism (PHPT) and hyperthyroidism secondary to toxic multinodular goiter (TMNG) is rarely described in the literature. Hereby, we describe the clinical, biological, and radiological characteristics of two patients having this rare association.
Observations
First case: A 66 years-old female was diagnosed with primary hyperthyroidism. Her thyroid antibodies were negatives. During the follow-up, she presented a high serum calcium level (2.95 mmol/l) and high Parathormone level (141.3 pg/ml) persisting after the correction of initial low 25-hydroxyvitamin D3. Her PHPT was complicated by osteoporosis and recurrent urolithiasis. Cervical ultrasonography and thyroid scintigraphy affirmed the presence of TMNG and bilateral lower parathyroid adenoma. She underwent a thyroidectomy and parathyroidectomy of the two adenomas. Histopathological examination confirmed the presence of a benign multinodular goiter (MNG) and two parathyroid adenomas. Second case: A 56 years-old female was followed-up for 18 years for MNG. She developed hyperthyroidism (FT4 = 35 mIU/l) followed by PHPT with hypercalcemia (2.79 mmol/l) and elevated Parathormone level (147 pg/ml) persisting after the correction of initial low 25-hydroxyvitamin D3. Her PHPT was complicated by osteopenia. Cervical ultrasonography and thyroid scintigraphy affirmed the TMNG without finding a parathyroid adenoma.
Conclusion
PHPT associated with thyroid nodules is rare. Hypercalcemia can be found up to a quarter of patients with hyperthyroidism. PHPT should be considered once hypercalcemia persists after correction of the thyroid status and parathyroid hormone should be determined.

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The thyrotoxicosis in patients with amiodarone induced thyrotoxicosis may not respond totherapeutic plasmapheresis like patients with Graves' disease

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Introduction
Due to the risk of thyroid storm, achievement of euthyroid state is necessary in patients with thyrotoxicosis undergoing surgery. However, euthyroid state could not be always achieved by antithyroid drugs. Therefore, therapeutic plasmapheresis (TPE) can be used for this purpose.
Case 1
A-58-year old male patient was admitted to emergency department with diabetic ketoacidosis (DKA) induced by amiodarone induced thyrotoxicosis (AIT). He had a history of Tip2 diabetes and ventricular arrhythmia which were treated with intensive insulin therapy and 200 mg amiodorone/day. His plasma glucose, arterial pH, serum TSH, fT3, fT4 and TRAb levels were 613 mg/dl, 7.19 log [H^+], <0.005 mIU/ml (0.4–4), 5.47 pg/ml (1.57–5.3), 5.3 ng/dl (0.8–1.9), 5.3 U/l (0–14), respectively. After appropriate treatment for DKA, propronolol 80 mg/day, methimazole 40 mg/day and methylprednisolone 60 mg/day were started. However, fT4 levels increased to >7.7 ng/dl 3 weeks after treatment. Therefore, thyroidectomy and preparation with TPE was planned. TPE was performed with plasma exchange method by Spectra Optia Apheresis System and %5 albumin and isotonic saline were used for replacement of plasma. After two sessions, fT4 and fT3 levels decreased only to 5.15 ng/dl and 2.22 pg/ml, respectively, consistent with a 35% decrease. A thyroidectomy was performed without any complication.
Case 2
A 74-year-old male patient with acute antertior myocardial infarction (AMI) induced by Graves' disease was admitted to emergency department. On biochemical analysis his serum TSH, fT3, fT4 and TRAb levels were <0.005 mIU/ml, 10.6 pg/ml, 4.5 ng/dl and 24 IU/l (0–14), respectively. Treatment with propranolol 80 mg/day, methimazole 40 mg/day and ten drops of lugol solution was started. A primer percutanous coronary anjiography revealed multiple vessel disease and an emergent coronary artery bypass grafting (CABG) was planned. So, a TPE was performed. After one session, fT4 and fT3 decreased to 2.48 ng/dl and 2.96 pg/ml, respectively, which were consistent with a 45% and 72% decrease in fT4 and fT3 levels. The patient underwent CABG surgery without any complication.
Conclusion
Although only one session of TPE was effective to achieve euthyroid state in a patient with Graves' disease, euthyroid state coud not be achived after two sessions of TPE in a patient with AIT. So, the thyrotoxicosis in patients with AIT may not respond to TPE like patients with Graves' disease.

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Effect of metformin therapy on thyroid stimulating hormone and BMI in hypothyroid egyptian patients

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Back ground and objectives
Relation between thyroid function with respect to insulin resistance has been a field that is rich and captivating for research and further examination. Few studies have suggested that metformin, the first-line in diabetes management, may lower thyroid-stimu-lating hormone (TSH). Owing to Paucity of studies regarding the effect of metformin on TSH in hypothyroidism patients, this study compares the effect of metformin on TSH and BMI in Egyptian naïve hypothyroid patients.
Methods
This cross-sectional prospective study recruited 200 patients with newly diagnosed hypothyroidism (86 male and 114 female). Patients divided in to two groups; Group 1 include 100 patients receive metformin 1000 mg beside thyroxine therapy and Group 2 (100 patients) treated only by thyroxine therapy. The height, weight, BMI, waist circumference (WC) and thyroid hormone levels were assessed at baseline and after 4 months of metformin treatment.
Results
BMI and WC decreased significantly after metformin therapy (27.8 ± 2.2, 97.2 ± 6.7) and (28.8 ± 1.8, 104.8 ± 5.4) ($P < 0.0001$) in group 1 vs group 2 respectively. No significant difference between two groups as regard to TSH ($P = 0.881$).
Conclusion
It has been established that metformin decrease body mass index and waist circumference in naïve hypothyroid Egyptian patients with no influence on TSH levels.

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IgM thyroglobulin autoantibodies are detectable in serum of patients with subacute thyroiditis

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Context
Subacute thyroiditis (SAT) is an inflammation of the thyroid, likely caused by a viral infection. IgG Autoantibodies (Ab) to the main thyroid antigens, including thyroglobulin (Tg) (TgAb) have been reported in a few patients with SAT and their appearance is usually transient. We investigated whether IgM TgAb can be detected in sera of patients with SAT.
Design
Serum samples were collected from 17 patients with SAT, ten with Graves' disease (GD) and 10 with Hashimoto's thyroiditis (HT). GD and HT sera were selected because of positive IgG TgAb (by AIA-PACK 2000, Tosoh Biosciences) . Samples of SAT patients were collected 1–9 months after the onset of SAT. IgG and IgM TgAb were measured in ELISA. Wells coated with human Tg were incubated with sera and IgG and IgM TgAb were detected with biotin-conjugated anti human IgG or IgM. HRPO- conjugated streptadivin was then added. The substrate was o-phenylene diamine $+H2O2$. ODs were read at 490 nm. To rule out non-specific binding, ELISA for IgM was performed with BSA, keyhole limpet hemocyanin (KLH) and glucagon (Gluc); sera showing BSA binding were considered as IgM TgAb negative.
Results
IgG TgAb were positive in 14/17 SAT, 10/10 GD and 10/10 HT. IgM TgAb were positive in 10/17 SAT, 0/10 GD and 0/10 HT. Seven SAT sera were IgG TgAb positive and IgM TgAb negative, 5 IgG TgAb negative and IgM TgAb positive and 5 IgG TgAb positive and IgM TgAb positive. Median titer was 1/100 (IQR: 1/33-1/1000) for IgG TgAb and 1/3300 (IQR: 1/3300-1/3300) for IgM TgAb. The duration of SAT did not correlate with positive IgM TgAb. All SAT sera did not bind KLH and Gluc in IgM ELISA.
Conclusions
IgM TgAb can be detected in sera of SAT patients with or without IgG TgAb. They do not correlate with the duration of SAT.

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P1029

Single session treatment of benign thyroid nodules with radiofrecuency ablation: results at 6 months in 17 patients

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Introduction
Radiofrecuency ablation (RFA) represents an alternative to surgery for benign thyroid nodules with pressure symptoms or evident progressive growth.
Objetives
To analyze in our center the efficacy and safety at 6 montns of a single session treatment of RFA performed in predominantly solid thyroid nodules.
Patients and methods
17 patients with citologically benign thyroid nodules with pressure symptoms (dysphonia, dyspnea, dysphagia, foreign body sensation) or evidence of growth ($>$ 2 mm in two diameters or $>$ 50% of volumen) who refused surgery were treated with RFA using the moving-shot technique. Patients were evaluated at month 1, 3 and 6 of the procedure. Porcentual change form the basal volumen, pressure symptoms,TSH, FT4, Tiroperoxidase antibodies and potential minor complications (hematoma, pain requiring analgesic medication) and major complications voice change, nodule rupture, thyroid disfunction and brachial plexus injury) were recorded.
Results
Mean basal volumen decreased from 26.6 ± 14.8 to 9.9 ± 9.1 ml at month 6 ($P < 0.05$). Percentage of volumen decrease was significant since the first month of RFA ($30.3 \pm 9.7\%$) reaching $58.8 \pm 21.1\%$ at month 6.Therapeutic success defined as more than 50% in volumen reduction was achieved in 11/17 cases. Presssure symptoms basally recorded in eight patients disappeared in all cases since the first month from RFA and antithyroid drugs could be removed in 2/3 patients with initial subclinical hyperthyroidism. There were no changes in hormonal and antibodies values. Minor complications were reported in ten subjects (five transient paint and five local minor hematomas)and there was only one major complication consistent with a nodule rupture observed at month 1 recovering spontaneously.
Conclusion
One single session treatment of RFA is an effective and safe outpatient procedure in shrinking thyroid benign predominantly solid nodules and in controlling pressure related symptoms. A second session of RFA and a better selection of candidate nodules (obviating those in a confluent nodule background) could improve the percentage of volumen reduction and the prorpotion of patients with successful ablation.

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P1030

Fibroblast growth factor 23 is elevated in patients with euthyroid Graves' disease

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Background
Graves' disease (GD) is associated with accelerated bone turnover and elevated fibroblast growth factor 23 (FGF23). FGF23 is involved in the mineral homeostasis, especially the regulation of serum phosphate. Literatures showed that FGF23 decreased along with treatment of GD. It remains unclear whether FGF23 becomes normal after euthyroid status achieved.
Methods
A total of 64 patients with euthyroid GD and 64 healthy control subjects were enrolled. Endocrine profiles including thyroid autoimmune profiles, FGF23 and bone turnover markers were obtained and compared between two groups and within each group.
Results
Euthyroid GD patients have significantly higher FGF23 and phosphate, and lower 25-hydroxyvitamin D (25OH-VitD) and intact parathyroid hormone (iPTH) levels than the control group. FGF23 was significantly and negatively correlated with phosphate level after adjusted for age, gender, calcium, iPTH and 25OH-VitD in euthyroid GD group.
Conclusion
Serum FGF23 levels remain higher than normal in GD patients even after euthyroid status achieved. Underlying mechanisms warrant further investigations. Data are presented as mean $\pm$ S.D. if the continuous variable is normally distributed, and as median (interquartile range) if not normally distributed. Corrected calcium was calculated as follows: serum calcium (mg/dL) $+0.8$ * (four – albumin). *P* values were calculated by t-test for continuous variables and by chi-squared test for categorical variables. FGF23 was log-transformed to become normally distributed for *t*-test.

Table 1 Clinical characteristics of study subjects.

	Euthyroid GD	Control	*P*
N	64	64	
Age (years)	47.6 ± 10.9	48.0 ± 10.8	0.8523
Gender (female: male)	51:13	50:14	0.828
Corrected calcium (mg/dl)	9.12 ± 0.48	9.23 ± 0.29	0.1874
Phosphate (mg/dl)	4.24 ± 0.78	3.84 ± 0.51	0.0044
25-OH Vitamin D (ng/dl)	16.40 ± 5.52	23.20 ± 5.24	<0.0001
iPTH (pg/ml)	15.39 ± 8.82	25.79 ± 11.25	<0.0001
FGF23 (pg/ml)	59.10 (45.18–95.09)	46.00 (27.21–60.55)	0.0003
PINP (ng/ml)*	49.70 ± 19.65	54.12 ± 20.65	0.5293
CTX (ng/ml)*	0.21 ± 0.12	0.23 ± 0.09	0.5995

*Data of PINP and CTX were analyzed in 23 euthyroid GD subjects and 13 control subjects.

Table 2 The relationship of FGF23 and phosphorous in linear regression model, using FGF23 as the dependent variable and serum phosphate as the independent variable.

	Euthyroid Graves' disease group	Control group
Crude		
Regression coefficient	−31.6	8.5
p value	0.015	0.260
Adjusted for age, gender, calcium, parathyroid hormone and 25-OH vitamin D		
Regression coefficient	−34.9	16.9
P value	0.045	0.306

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Evaluation of the iodine sufficiency of pregnant women in Belarus

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Republic of Belarus belongs to the iodine-sufficient countries. However, the subject of the study is to assess iodine status of pregnant women as the critical group of the population. Iodine deficiency has a negative impact on the level of pregnancy complications and childbirth, increasing the risk of babies with low birth weight, adverse effect on newborn and children of early age health.
The purpose of this study
To assess iodine sufficiency of pregnant women in 2nd trimester of pregnancy (random sampling).
Material and methods
The study included 100 pregnant women in the 2nd trimester of pregnancy. For an objective assessment of iodine status the following methods were used: estimation of urinary iodine excretion (by spectrophotometric cerium arsenite method adopted by the WHO) and thyroid dimensioning and estimation of iodine supplements (%).
Results
The table shows results for urinary iodine concentration in pregnant women.

Table 1

	The distribution of patients (%) in urinary iodine concentration (μg/l)						Me UIC,	Me, thyrod gland
Number	<20	21–50	51–100	101–250	251–300	>300	μg/l	volume, ml
100	0	6	33	23	11	27	157.3	16.4

The results indicate that only 38% of pregnant women reach the target level of urine iodine excretion. This value is consistent with the questionnaire data, which indicates that only 47% of pregnant women take potassium iodide, despite the recommendation of taking iodine-containing drugs to all pregnant women. The median thyroid gland volume corresponds to the normal values, which indirectly indicate a short period of iodine insufficiency.
Conclusion
Despite the achievement of target levels of iodine sufficiency in a population of children and adults, it is necessary to use of potassium iodide in pregnant women.

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Thyroid disease in PHPT: a single centre study

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Objective
Primary hyperparathyroidism (PHPT) and thyroid diseases are common in the general population. It is difficult to establish whether they occur in the same patient because of a direct relationship or just due to the widespread prevalence of both conditions. The reported prevalence of the concomitant occurrence of these two clinical conditions is widely scattered (ranging 17–84%), especially due to the heterogeneous criteria for patient selection. We aimed to evaluate in a large series of PHPT patients the prevalence of thyroid diseases and the clinical and biochemical presentation of PHPT in patients without or with concomitant thyroid diseases.
Methods
We retrospectively evaluated an unselected and monocentric series of 434 outpatients with PHPT, attending our hospital between 1998 and September 2017. Patients with neither bone or kidney involvement, nor hypercalcemic symptoms were considered asymptomatic. The US thyroid pattern was considered abnormal if nodules or features of chronic lymphocytic thyroiditis were found. The histological report of patients submitted to thyroidectomy was then evaluated.
Results or Case Presentation
Thyroid diseases were found in 263/434 (60.6%) PHPT patients. Among them, over than 80% were affected by nodular goiter, that was toxic in almost 10% of cases. Thyroid autoantibodies were positive in 50 (19%) patients, all with an autoimmune US pattern. Thyroid cancer was diagnosed in 11/85 patients (12.9%) and it was a papillary microcarcinoma in all cases but one. Patients with thyroid diseases were older and more frequently female than the others, despite no difference in serum calcium, creatinine, 25OHD and TSH levels. PTH levels result significantly higher in patients without thyroid abnormalities. Anyway, no difference were found in the PHPT clinical presentation nor in the presence of osteoporosis at any site between the two groups.
Discussion
Thyroid diseases, mostly nodules, were present in 60% of our patients with PHPT,consistently with the goiter endemic area where our study has been conducted. Moreover, a thyroid carcinoma was found in more than 10% of patients. The predominantly histotype was papillary microcarcinoma, in agreement with literature data. PHPT characteristics resulted biochemically and clinically similar in patients with or without thyroid abnormalities.
Conclusion
In conclusion, the majority of PHPT patients have a thyroid disease. Our data confirm that thyroid diseases and PHPT are two conditions prevailing in specific population, thus making their association more frequent. Thyroid nodules could interfere in the diagnostic and therapeutic PHPT work up.

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Clinical importance of incidentally discovered thyroid nodule by carotid artery ultrasonography

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Thyroid nodules were frequently incidentally discovered during radiologic studies of chest or neck. We investigated the prevalence and clinical importance of thyroid incidentaloma during carotid artery ultrasonography in patients with diabetes. We retrospectively reviewed the data of enrolling all diabetic patients who were performed carotid artery ultrasonography at the Diabetes Center of Wonju Severance Christian Hospital from January to December 2013. Chart reviews of all eligible patients were performed. For those diagnosed with thyroid nodules, ultrasonographic findings and diagnosis of the thyroid nodules were reviewed. Total subjects enrolled this study were 1,518 patients and mean age was 59.98 ± 11.15 years. The prevalence of thyroid nodules discovered by carotid artery ultrasonography was 46% (803 of 1,518) and total 1,542 thyroid nodules were seen in the study. In these thyroid nodules, 157 cases (10.2%) were underwent fine needle aspiration biopsy (FNAB). The results of diagnosis of fine needle aspiration biopsy were benign 73%, atypical cells with unsignificance 12.6%, papillary carcinoma 6.3%, and material insufficiency 8.2%. The prevalence of thyroid nodule was linearly increased by age. Routine carotid IMT measurement in diabetic patients may discover thyroid nodules more frequently than in healthy population, so clinicians should pursue further investigation of these nodules by clinical guidelines for thyroid nodules.

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Thyroid function in relation to pregnancy outcome

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Introduction
Thyroid disease in pregnancy is a common clinical problem, at least 2–3% of women have thyroid dysfunction, and it is estimated that about 5–20% of women of reproductive age suffer from autoimmune thyroid disease. Subclinical thyroid disease during pregnancy may be associated with adverse outcomes. In the first trimester, the 'normal' range for TSH 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, and determine thyroid function in relation to pregnancy outcome.
Matherial 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 fT4, TSH and TPOAb and measured by RIA method. As parameters of adverse outcomes we included: premature labor (before 37 gw., Low Apgar score (<8), neonatal malformations, respiratory complications, hypoglycemia, birth body weight $>$ 4000 g or $<$2500 g, hyperbilirubinemia
Results
The mean age of patients was 30.8 ± 4.7 years. The prevalence of autoimmune thyroid disease was 25.9%, positive family history for thyroid disorder was in 9%, smoking in 23.4% patients. The average serum level in patients with adverse outcomes ($n=41$) for fT4 was 10.7 ± 2.46 pg/ml, for TSH was 2.52 ± 1.1 mIU/l, and for TPOAb was 737, while in group with a favorable outcome ($n=36$) average serum level for fT4 was 10.2 ± 2.1 pg/ml, for TSH was 2.25 ± 1.2 mIU/l, and for TPOAb was 474. It has been shown that the number of risk factors significantly affect the outcome of pregnancy ($P<0.005$, χ^2 test), and that the presence of TPOAb as marker of autoimmune thyroid disease during pregnancy affect the outcome of pregnancy (24,4% patients with a favorable outcome and 27,7% patients with adverse outcomes had positive TPOAb). It has been shown that patients without TPOAb usually have a favorable outcome of pregnancy, and a growing number of pregnancies with an adverse outcome in patients with TPOAb.
Conclusion
This study demonstrates that the presence of TPOAb as marker of autoimmune thyroid disease during pregnancy predicts unfavorable adverse outcome.
Keywords: thyroid function, pregnancy, outcome

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P1035

The assessment of vitamin D3 deficiency in patients with Hashimoto's disease and the relationship between the disease duration and 25OHD3 levels

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The observed increase in the incidence of Hashimoto's thyroiditis (HT) requires the research on environmental factors that may initiate or model its course. There have been reports of the impact of vitamin D3 deficiency on HT development.
Objective
To assess the degree of deficiency of 25OHD3 and the relationship between the disease duration and 25OHD3 levels in patients with HT.
Material and methods
310 people were enrolled in the study: 155 patients with HT-144 women (93%), 11 men (7%) and 155 healthy volunteers-139 (90%) women and 16 men (10%); mean age: 49 ± 18, 58 ± 17, 49 ± 17 and 56 ± 16 years respectively. Serum 25OHD3 concentration was measured in all subjects. The relationship between HT duration and 25OHD3 concentrations was evaluated in HT group. The analysis was also performed in HT subjects and the disease duration of $<$ 1 year and $<$ 2 years. Vitamin D deficiency was defined as 25OHD3 $<$ 30 ng/ml.
Results
In HT patients 25OHD3 level was lower than in the control group: 23.2 ng/ml (Q_1-Q_3: 18.6-29.0) vs 25.6 ng/ml (Q_1-Q_3: 21.0–31.4; $P=0.006$).There was a significant correlation between the disease duration and 25OHD3 concentrations in HT patients ($R=-0.32$; $P<0.001$). The correlation was moderate and negative. The regression coefficient of impact the disease duration on the mean 25OHD3 values in the HT group was -0.615. The adjusted coefficient of determination was 8.4%. Analysis in HT group and duration of disease $<$ 1 year ($n=30$) and $<$ 2 years ($n=46$) showed no significant correlation between duration of HT and 25OHD3 concentrations respectively: $R=0.23$; $P=0.223$; and $R=0.16$; $P=0.295$.
Conclusions
Vitamin D3 deficiency is more prevalent in HT patients, and may adversely affect and enhance the abnormal response of the autoimmune process in later stages of the disease without significant impact of its initiation.
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P1036

Hypothyroidism treated with weekly intramuscular thyroxine injections

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Background
Oral levothyroxine (LT4) is usually an effective treatment for hypothyroidism. However, timing of meals, concurrent medications and gastrointestinal diseases causing malabsorption may impair absorption of oral LT4. We present a patient with Hashimoto's thyroiditis on LT4 replacement through a gastrostomy tube causing the problem of erratic thyroid function test (TFT) results, successfully managed through the use of once-weekly intramuscular LT4 injection.
Clinical case
A 65-year-old Chinese male was on follow-up with our clinic for multi-nodular Hashimoto's goiter requiring thyroxine replacement, 125ug/d, resulting in serum free thyroxine (fT4) 15 pM (RR 8–21 pM), and thyroid stimulating hormone (TSH) 1.12 mIU/L (RR 0.34–5.6 mIu/L). His co-medications were aspirin, famotidine, lisinopril, atenolol, trimetazidine and simvastatin. He was diagnosed with squamous cell carcinoma of the tongue and lip in 2006, requiring multiple surgeries, radiotherapy and eventually on 24/2/17, permanent gastrostomy tube feeding. However, he experienced multiple episodes of blocked gastrostomy tube due to luminal obstruction by residual feeds requiring urgent tube change. Despite a body weight of 50kg (BMI 19.1 kg/m2), the patient required increasing doses of levothyroxine up to 100mcg daily. Despite the high dose of levothyroxine, he continued to experience fluctuating fT4 levels, ranging from 4 to 13 pM, and TSH levels, ranging from 2.04 to 69.52mIU/L. As he was compliant and administered his doses of medication correctly through the PEG (via crushing of tablets and suspension in plain water), we hypothesized that his labile TFT results were due to poor enteral delivery of LT4 through the gastrostomy tube. Thereby on 16/11/17, the patient was started on intramuscular LT4 400mcg injection once weekly. At the 8th cycle, serum fT3, fT4 and TSH levels were measured pre-dose (trough), 4 hours post-dose (peak), and on day 1, day 3 and day 6.

	UoM	Trough	Peak	Day 1	Day 3	Day 6
fT3	pmol/L	3.9	3.7	3.7	3.8	3.5
fT4	pmol/L	8	15	13	11	9
TSH	mIU/L	30.06	20.86	9.66	17.91	26.25

His fT3 levels remained stable throughout the entire duration. His trough fT4 of 8 and peak fT4 of 15 were adequate and appropriate. He remained free of symptoms of hyperthyroidism and hypothyroidism and reported no side effects from the intramuscular levothyroxine regime.
Conclusion
This case demonstrates that in hypothyroid patients with impaired enteral delivery of LT4, once-weekly intramuscular injection of LT4 can safely and effectively provide stable serum fT4 and fT3 levels.
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P1037

Evaluation of thyroid nodule, volume and arterial stiffness in euthyroid individuals

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Aim
Overt/subclinic hypothyroidism and hyperthyroidism are known to be associated with cardiovascular risks. There have been no studies evaluating the relationship

between nodule presence and arterial stiffness in individuals with euthyroid nodular goitre. Our aim in this study is to demonstrate whether nodule presence and nodule stiffness affect arterial stiffness in individuals with euthyroid nodular goitre by using pulse wave analysis (PWA).
Materials and methods
In our study, 50 patients with eutyhroid nodular goitre and 50 healthy volunteers were included. All participants were evaluated by B-mod thyroid ultrasonography (USG) and the individuals in the nodular goiter group were also performed strain elastography (SE) by one experienced radiologist. Strain indices of nodules classified according to Rago scoring system were calculated. As well as waist and hip circumference, insulin, fasting plasma glucose (FPG), lipid parameters, free T3(sT3), free T4(sT4), TSH, anti-thyroglobulin antibody (anti-TG) and anti-thyroid peroxidase antibodies (TPO) levels were measured. The levels of insulin resistance calculated by homeostasis model assessment-IR(HOMA-IR) were evaluated. Evaluation of arterial stiffness was performed with the Mobile-O-Graph 24h PWA device.
Results
When comparing two groups with respect to data of PWA, pulse wave velocity was found to be statistically significantly higher in the group with nodular goitre ($P<0{,}001$). Other data of PWA were similar among the groups. There was no difference in HOMA-IR and insulin levels between the two groups. FPG levels were higher in the group with nodular goitre ($P=0{,}03$). There was no correlation between HOMA-IR and thyroid volume, nodule volume, nodule number ($P>0{,}05$). Also, correlation was not seen between HOMA-IR and strain index and data of PWA.
Conclusion
Detection of high levels of pulse wave velocity and fasting plasma glucose in patients with nodular goitre suggests that individuals with euthyroid nodular goitre should be followed closely for cardiovascular and metabolic risks.
Keywords: euthyroid nodular goitre, insulin resistance, strain index, pulse wave velocity

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P1038

Iron deficiency, a risk factor for thyroid dysfunction and autoimmunity in the second trimester of pregnancy in China

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Ferritin is a universal intracellular protein that acts as an iron carrier. Several studies have indicated that iron deficiency affects thyroid function in non-pregnant women. Our objective was to assess the relationship between serum ferritin levels and thyroid function along with thyroid autoimmunity in pregnant women during the second trimester. 1592 pregnant women were recruited from the obstetric outpatient department during the second trimester. Serum ferritin (SF) levels, thyroid function, TPOAb and TGAb were determined by electrochemiluminescence immunoassay. Age, BMI and pregnant week were recorded. Iron deficiency (ID) was defined as ferritin <12 μg/L, and subclinical hypothyroidism (SCH) when TSH was >4 mIU/L. The percentage of ID and SCH were 11.87%, 9.17% respectively. Serum FT4 levels were significantly lower in the ID group as compared with the non-ID group [13.82(8.91–25.04) vs 14.60 (8.22–47.24) mIU/L; $P=0.000$],TSH levels were similar in the ID and non-ID group [1.78(0.01-7.13) vs 1.71 (0.01–10.2) pmol/L; $P=0.520$] and The prevalence of abnormal elevated TPOAb and/or TGAb, and SCH were comparable between both groups. SF levels were negatively correlated with serum TSH levels ($r=-0.112$, $P=0.000$), and positively correlated with FT4 levels ($r=0.201$, $P=0.000$). Linear regression analysis showed SF, age, week of gestation were significant predictors of regression with TSH as the dependent variable (β: -0.002, -0.026, and 0.061 respectively; all $P<0.05$), or with FT4 as the dependent variable (β: 0.005, -0.054, and -0.24 respectively; all $P<0.05$). Interestingly, in the logistic regression model, ID remained associated with abnormal elevated TGAb after correction for confounding factors [OR = 2.84, 95%CI (1.385, 5.825), $P=0.004$], but not correlated with abnormal elevated TPOAb. Therefore, maternal ID was a determinant of higher serum TSH, lower FT4 levels, and abnormal elevated TGAb in pregnant women during the second trimester.

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P1039

A rare case of amyloid goiter with concomitant papillary thyroid microcarcinoma in a patient with HIV

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Introduction
Amyloid goiter (AG) may be associated with either primary amyloidosis (deposit of amyloid protein AL) or secondary amyloidosis (deposit of amyloid protein AL) in chronic inflammatory diseases including tuberculosis, cystic fibrosis, ulcerative colitis, ankylosing spondylitis and familial Mediterranean fever. To our knowledge, this is the first case of AG concomitant with PTC in a patient with HIV infection.
Case presentation
67-year-old male immigrant from Somalia with past medical history of HIV with CD4 count of 427/ml complained of painful progressive enlargement of neck mass for three months with dysphagia, dyspnea on exertion associated with weight loss and generalized weakness. A diffuse non-tender asymmetrically enlarged goiter was palpated with no cervical lymphadenopathy. Ultrasonography revealed diffusely echogenic heterogeneous significantly enlarged thyroid gland without discrete cystic or definable mass. Right lobe measured $96\times38\times58$mm, left lobe $76\times38\times42$mm, and Isthmus 20mm. Free T4: 0.93 ng/dl (0.80–1.80ng/dl), TSH: 0.067 munit/ml(0.40–5.00), TSI:151%(0–139). CT showed asymmetric enlargement of the right thyroid lobe and isthmus with deviation of the trachea and esophagus without retrosternal extension or significant cervical lymphadenopathy. FNA showed deposition of AA Amyloid localized in thyroid gland with positive Congo red staining. Surgical pathology revealed the same in addition to a small focus of 0.3 cm PTC. Further evaluation confirmed that patient's amyloidosis is localized only to thyroid without systemic involvement.
Discussion
Endocrinopathy is well recognized in relation to HIV infection itself or as a side effect from HAART. However, the association of HIV infection with AG is not well established. The patient presented in this case has AG localized amyloid deposition in thyroid gland without systemic amyloidosis and no clear chronic inflammatory condition other than HIV infection. Another unique feature is the presence of PTC as apposed to what has been described of AG being mostly associated with medullary carcinoma. There is no specific treatment for AA amyloidosis but treating primary underlying condition can halt the progression. Due to compressive symptoms, surgery was offered in this case.
Conclusion
AG should be included as differential diagnosis of rapid enlargement of thyroid gland in HIV patients.

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P1040

A thyroid hormone-independent molecular fingerprint of 3,5-diiodothyronine suggests a strong relation with coffee metabolism in humans

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Background
Numerous animal models have shown impressive beneficial metabolic effects of the putative thyroid hormone (TH)-derivative 3,5-diiodothyronine (3,5-T2),

including the prevention of insulin resistance or the reversal of hepatic steatosis, in the absence of thyrotoxic side effects. In contrast, the endogenous fate of 3,5-T2 in humans is still unclear. Comprehensive molecular profiling holds promise to gain deeper insights in metabolic alterations associated with serum 3,5-T2.
Methods
Among 856 participants of the Study of Health in Pomerania (SHIP-TREND) serum 3,5-T2 concentrations determined by chemiluminescence immunoassay were available. Metabolomics data were obtained using mass spectrometry and nuclear magnetic resonance spectroscopy, comprising 613 and 578 metabolites in plasma and urine, respectively. Linear regression analyses with either continuous or categorized 3,5-T2 concentrations were used to detect significant associations. Controlling for age, sex, waist circumference, thyrotropin and free thyroxine allowed assignment of thyroid function independent effects. Results were replicated in an experimental model of thyrotoxicosis comprising 16 male volunteers.
Results
Serum 3,5-T2 concentrations were not associated with thyroid function parameters nor altered during experimental thyrotoxicosis. The molecular fingerprint of 3,5-T2 comprised 15 and 73 significantly associated metabolites in plasma and urine, respectively. Metabolites related to coffee metabolism, including caffeine or paraxanthine, represented the most obvious molecular signature. This association was replicated under experimental thyrotoxic conditions.
Conclusion
The TH-independent molecular fingerprint of serum 3,5-T2 concentrations showed a clear and strong interference with coffee metabolism and points to the liver as potential target organ in the focus of local 3,5-T2 generation/action. Translating the beneficial effects seen in animal models, 3,5-T2 might provide a link between (high) coffee consumption and the decreased risk of metabolic diseases.

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P1041

The benefits of the thyroid disease screening program in pregnant women in Slovakia

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Objectives
Screening of thyropathies in Slovakia began in 2009 on the basis of the expert guideline of the Ministry of Health of the Slovak Republic for the diagnosis and treatment of autoimmune thyroid diseases in women during pregnancy (Public Health Ministry 39, 2009, No. 33–39)
Methods
The records of pregnant women insured by the health insurance company Dôvera, who had their first documented gynecological visit due to pregnancy in 2011, while they had no records of an endocrinology visit in 2010. Women had blood taken for TSH and aTPO at the gynecologist and were subsequently examined by an endocrinologist, were involved in the study. An individual group that was monitored by an endocrinologist under diagnoses E.00 to E.07 by the end of 2013.
Results
Overall, 13,876 pregnant women insured by the health insurance company Dôvera, a.s. (27.50 market share) who have undergone the first examination in 2010 with confirmed pregnancy, were registered. Of this group 294 (2.19%) had a record of repeated endocrinology visit with dg. E.00 to E.07. 5,143 (37.06%) of 13,876 women women had blood taken for TSH (aTPO could not be identified), and 275 (5.35%) had at least two endocrinological examinations by the end of 2013. In 2011 207 (75.50%) women were prescribed at least 1 pack of thyroxin, in 2012 151 women (55.11%) and in 2012 195 women (70.80%). Of the thyreostatic drugs - thiamazole a prescription was documented only in two cases (0.70%) in 2013.The total cost for 2011-2013 was € 114,915. The cost of one case of the screening of trapped thrombotic pathology was € 399.50, the cost of one case of treated hypothyroidism was € 638.70. The cost for 1 case of hyperthyroidism was € 57,457.5.
Conclusions
The screening of thyroid pathology, evaluated in the 2 years of the MZ SR expert's guide, show its low feasibility by gynecologist in the population of pregnant women - 37.06%. The prevalence of documented thyreopathies in pregnant women was found to be 2.19%, while the prevalence of newly diagnosed thyreopathies was 5.35%. The overall prevalence of thyropathy in the 30–35 year-old women category can be estimated at about 7.54%. From newly diagnosed thyreopathies was in the first year after the detection of thyreophaty therapy needed in 70%–76%. An identical study for the years 2016–2017 is planned to assess the state of the screening program after 5 years.

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P1042

Level of awareness in hypothyroid patients

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Aims
Hypothyroidism is a common disease and important in terms of community health. To increase the awareness of patients is an important issue in the healthcare process. In this study, it was aimed to determine the level of awareness and the factors affecting the awareness in the patients with hypothyroidism.
Methods
A questionnaire was conducted to patients diagnosed with hypothyroidism who were applied to the Okmeydanı Education and Research Hospital internal medicine and endocrinology outpatient clinics, aged over 18 years, diagnosed at least three months ago, had no thyroid malignancy and weren't pregnant. The relationship between awareness level and follow-up/treatment parameters and sociodemographic characteristics is examined.
Results
A total of 258 patients were included in the study, 221 (85.7%) female and 37 male (14.3%). The mean age was 53 ± 14.3 years and the TSH mean level was 5.8 mIU/l. The majority of the participants were primary school graduates, low-income and have disease duration over 5 years. There was no statistically significant difference between the number of total correct answer and follow-up frequency, family history of thyroid disease, marital status and smoking status ($P > 0.05$). There was a statistically significant difference between the level of awareness and age, sex, education level **and** income level ($P < 0.05$). The younger age group with higher education and income levels answered more questions correctly, a higher level of awareness was found in female patients. 54.7% of patients answered more than half of the questions incorrectly. While 70.5% of the participants knew the definition of hypothyroidism, only 42.6% had information about iodine deficiency. The rate of those who knew that thyroid replacement should not be stopped during pregnancy was 27.5% and who knew that thyroid hormones affected fetal intelligence development was 21.7%. Patients considered that levothyroxine should be used in the morning (84.1%) and on an empty stomach (88.4%), while they thought that it could be used in combination iron products (72.1%) and proton pump inhibitors (64.7%).
Conclusions
As a result of our study, it was concluded that there is not enough level of awareness about the diseases in hypothyroid patients. In order to increase the level of awareness, it has come to the conclusion that there should be a period of time for informing during the outpatient visits and this process should be supported by other methods like web pages, brochures, patient education programs, media programs.

Keywords: hypothyroidism, level of awareness, questionnaire
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P1043

Predictive value of HLA variants for Graves' disease recurrence – pilot study in Czech patients

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Introduction
Graves' disease (GD) is the most common cause of hyperthyroidism. The first-choice therapy is administration of thyreostatic drugs. However, approximately half of patients relapse within two years of discontinuation. It is then necessary to decide whether to re-initiate thyreostatic treatment, which may have serious side effects, or to choose a radical approach (TTE, radioiodine). Familial forms of GD indicate that the disease has a significant genetic component. The autoimmune nature of GD refers to the human leukocyte antigen complex (HLA). Within HLA, some variants of DRB1, DQA1 and DQB1 genes appear to be possible predictors of GD development and recurrence. The aim of our work was to introduce a reliable methodology for testing the HLA background of GD. Assessment of its predictive potential on the disease recurrence in long-term follow-up would make it easier for physicians and patients to choose an optimal therapeutic approach.
Methods
In 50 patients treated in the Institute of Endocrinology with GD, the sequencing was chosen as the most reliable haplotyping method. In the three HLA candidate genes (DRB1, DQA1 and DQB1), exon 2 was amplified as the part of the HLA molecule determining its antigenic properties. Amplification of DNA sequences required the group-specific S2, S3 and S4 kits (PentaGen, Protrans - Germany). NGS was performed on MiSDefault (Illumina).
Results
Concerning the patients with recurrence ($n=24$), the predisposing allelic groups were equally distributed ranging from no risk allele to four risk alleles. Unfortunately, patients who have not yet relapsed and whose remission lasts for more than 2 years are represented by only two individuals, one carrying no risk allele and the other carrying one risk allele. Fisher's exact test identified allelic group DQA1*05 to be close to statistical significance in terms of the ability to predict the recurrence ($P=0.06$). The remaining patients in the current cohort ($n=24$) can not yet be included in the statistical analysis as they are still being treated or their remission period has not yet reached two years of duration.
Conclusion
We reliably classified the HLA DRB1, DQA1 and DQB1 allelic groups in first 50 patients with GD. Low number of patients in long-term remission does not yet allow to quantify the allele-associated risk of the disease relapse. However, the DQA1*05 appears to be the most promising recurrence predictor.
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P1044

Usefulness of ultrasound evaluation of thyroid nodules in predicting malignancy

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Introduction
Ultrasound (US) thyroid examination is the most common method to assess thyroid nodules risk of malignancy and select nodules for fine-needle aspiration biopsy (FNAB). Thyroid US evaluation performed by endocrinologists has recently increased in Spain.
Objectives
To evaluate the predictive value of US features of malignancy in differentiating benign and malignant thyroid lesions in a Thyroid Nodule Clinic.
Patients and methods
Retrospective analysis of 296 patients referred to an Endocrinology Department for US thyroid nodule evaluation, between October 2016 and October 2017. US features assessed in each nodule were: size, hypoechogenicity (HE), shape taller than wide (T > W), irregular margins (IM), intranodular vascularity (IV) and microcalcification (MC). A total of 337 nodules were selected for FNAB and were classified based on the Bethesda system. Thirty-three cases with Bethesda categories different from benign without histological diagnosis, were excluded for accuracy study. The sensivity (Se), specifity, negative (NPV) and positive (PPV) predictive value and accuracy of US features were evaluated.
Results
A total of 296 patients (250 women), median age 55 years old were included. TSH median was 1.6 mcUI/ml, 31% with positive thyroid antibodies. The median nodule size was 1.8 cm. In 119 nodules (35%) there were no sonographic malignancy features. In these cases, the US assessment of malignancy had a NPV of 99%. In 218 nodules (65%) there was one or more US malignancy feature: HE (42%), T > W (5.6%), IM (15.7%), IV (22%) and MC (12%).A Hypoechogenicity had the highest Se (56%) but its PPV was low (7%). Microcalcification had the highest PPV (19.4%) for malignancy diagnosis with a Se 37.5%.
Conclusion
Nodules with at least one US malignancy feature, specially microcalcification, should undergo FNAB. In nodules without any US malignancy feature, histological malignancy diagnosis is highly improbable.

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P1045

Ultrasound in stages of surgical treatment of patients with thyroid diseases

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The results of Surgeon-Performed Ultrasound before and after operations have evaluated at the 207 patients with pathology of the thyroid gland. Comparative assessment made between ultrasound at out-patient phase and Surgeon-Performed by ultrasound. Ultrasound at the outpatient stage in the screening mode does not provide a sufficient level of diagnostics. Causes of errors at this stage are a short time of the inspection, insufficient expertise, wrong interpretation of the image ignorance of the standards of diagnosis, lack of the resolution of the instrument, the subjectivity of assessment, depending on the qualification and integrity of the doctor. It is established that regardless of the nature of thyroid diseases carried out by the preoperative Surgeon-Performed Ultrasound has better results in comparison with the outpatient stage: fewer differences with the real picture when assessing the volume of the organ, the size, number and localization of nodules. Accounting surgeon features of the structure and location of the thyroid gland gives him the opportunity of planning the operation with minimal trauma to the patient. Conducted Surgeon-Performed Ultrasound of the organs of the neck in addition to the standard Protocol included inspection of the larynx. Ultrasonography of the larynx (for her vizualisation) before operation allowed to take into account the preconditions for the development of complications and to identify already existing pathological changes. Surgeon-performed ultrasound examination in the early postoperative period can visually assess the dynamics of wound process, to identify complications of the soft tissues and eliminate them. Ultrasound allows to objectively assess the condition of the abandoned tissue of the thyroid gland in organ-saving operations. Surgeon-Performed Ultrasound of the larynx in the postoperative period allows the high percentage of reliability to detect in the early stages of paresis of the larynx.

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P1046

Active surveillance of indeterminate thyroid nodules beyond cytological diagnosis, ultrasound evaluation and molecular analysis

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Most thyroid nodules are benign after fine needle aspiration biopsy (FNAB). Nevertheless approximately 10–25% of nodules are classified in indeterminate classes. Literature reports different risks of malignancy in Thy 3 – Thy 4 nodules. In our center malignancy was observed in 26% of Thy 3a nodules and 14% of the Thy 3f nodules (Giusti *et al.* 2017) while it was >75% in Thy 4 nodules. Strategies for nodules stratification according to risk are now needed to reduce thyroidal surgery. The aim of the study was to report results of active surveillance in Thy 3 nodules in which thyroidectomy was refused or delayed. Sixty-five nodules (patients) with indeterminate thyroid cytology at the 1st FNAB ($n=33$ Thy 3a, $n=12$ Thy 3f, $n=10$ Thy 3) underwent active surveillance. Active surveillance includes: calcitonin and thyroid blood tests, neck ultrasonography (US), elastosonography (USE), contrast enhanced US (CEUS), BRAF mutation analysis and a 2nd FNAB. BRAF analysis was negative in all nodules and all

patients showed normal hormonal levels. At present the active surveillance period is of 48 months. Eight of the 65 nodules receded from surveillance for thyroid surgery ($n=1$: 1 NIFPT; 1 follicular adenoma), severe cardiac failure ($n=1$), change of geographical area ($n=1$) or retire of consensus ($n=4$). Twelve patients (18%) did not perform/refused 2nd FNAB. The 2nd FNAB showed down classification to Thy 2, stable Thy 3 category and subcategories, and non-diagnostic information in 64%, 29% and 7%, respectively. US score doesn't show significant changes from the baseline ($n=65$; 1.95 ± 1.08) compared to the last examination ($n=38$; 1.87 ± 1.07). In average, nodules were not significant in maximal diameter from the baseline (25 ± 12 mm) compared to the last examination (23 ± 13 mm) even if in 16% of nodules there was a change ($>20\%$) in size [increase (10%), decrease (6%)]. All the nodules with an increase in size were Thy 2 at the 2nd FNAB evaluation. USE and CEUS did not add further information after inclusion of patients under active surveillance. In conclusion our prospective study suggest that active surveillance can be proposed to patients with indeterminate cytology when no BRAF mutation is found from FNAB. The down classification to Thy 2 class is a frequent phenomenon when further information and material are collected for the pathologist. Simple changes in diameter of the nodule do not suggest surgical decision. However more data need to be collected.

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P1047

A case of subacute thyroiditis associated with adalimumab

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Subacute thyroiditis is a painful disease of the thyroid gland characterized with granulomatous inflammation. Adalimumab is a human monoclonal anti TNF antibody used in the treatment of several autoimmune diseases. Here we report a case of subacute thyroiditis associated with adalimumab treatment for ankylosing spondylitis. A 42 year old female patient was admitted to the hospital for fever, chills and neck pain radiating to the right ear. She was diagnosed with ankylosing spondylitis 9 years ago and was on adalimumab treatment (40 mg every 15 days) for the last 7 years. On physical examination her body temperature was 38.2 °C. Thyroid was diffusely enlarged and tender to palpation. Laboratory evaluation of the patient is summarized in table 1. A thyroid scintigraphy showed a diffusely supressed gland. Ultrasonography of the thyroid revealed diffuse enlargement of the gland with interspersed hypoechoic areas (figures A and B). The patient was diagnosed with subacute thyroditis. Serum Ig M for CMV and EBV were negative. Adalimumab treatment was stopped and prednisolone 32 mg/day was started. Four weeks later, she consulted again with relapse of fever and neck pain due to noncompliance with the steroid treatment. She was hospitalized and 48 mg/day prednisolone was given. Her neck pain subsided and her fever responded dramatically to steroid treatment. She was discharged on steroid treatment. When the patient came for a control at 6 weeks her thyroid function tests were normal and CRP decreased to 5.6 mg/dl. Adalimumab is a biologic agent used in the treatment of autoimmune diseases. To date three cases of subacute thyroiditis are reported with adalimumab. Subacute thyroiditis is histopathologically characterized with granuloma formation. TNF-α plays an important role in regulation of T cell function and granuloma formation. Adalimumab is implied in the paradoxical development of pulmonary sarcoidosis and granulomatous skin reactions.The precise mechanism underlying the association between adalimumab and the onset of subacute thyroiditis remains unclear.

Table 1 Laboratory values of the patient at diagnosis.

C reactive protein	132 mg/dl
ESR	56 mm/h
WBC/PMNL	15,700/mm^3/83.4%
TSH	0.09 mIU/l
Free T3	3.78 ng/l
Free T4	1.72 ng/dl
Anti TPO	9.0 IU/ml
Anti TG	18.14 IU/ml
Thyroglobulin	500 ng/ml

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P1048

Correlation of recommended diagnostic tools with pathological findings in the thyrotoxic patient

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Aim
A key diagnostic step to determine the cause of hyperthyroidism is the measurement of circulating thyroid-stimulating immunoglobulin (TSI). High levels are associated with Graves' disease (GD). A thyroid scintigraphy (TRS) is recommended when TSI is absent or its measurement unavailable, as TRS is capable of differentiating between GD (diffuse uptake) and toxic goitre (TG) (patchy uptake). Nevertheless, and while rarely necessary, histopathology remain the best method for obtaining an accurate aetiology. Our purpose was to compare TSI vs. TRS sensitivity and specificity in the differential diagnosis of thyrotoxicosis.
Methods
We retrospectively studied 235 outpatients with hyperthyroidism (overt or subclinical) admitted in our Centre from 2006 to 2016 from whom TSI and TRS were performed at the time of diagnosis. Subsequently, we selected a sample of thyroidectomised patients in whom a histological specimen was available. A pathologist reviewed the samples. SPSS 23.0 was used for statistical analysis. Pearson's correlation was used to quantify the relationship between the diagnostic tests.
Results
A total of 45 patients met the inclusion criteria. We divided the sample according to the histopathology diagnosis of GD: Group A: 14 patients (31.1%) consistent with GD; Group B: 31 patients (68.9%) without features of GD. In Group A, one patient (7.1%) had negative TSI and two patients (14.3%) did not have a TRS with a high diffuse uptake. In Group B, 10 patients (32.2%) had positive TSI and 6 patients (19.3%) had a TRS with a high diffuse uptake. In comparison with histopathology, the TRS yield offered better diagnostic precision than TSI in both accuracy (82.2% vs. 75.5%) and specificity (80.6% vs. 67.7%) although inferior sensitivity (85.7% vs. 92.8%). The Positive Predictive Value (PPV) for TSI was 56.5% and the Negative Predictive Value (NPV) was 95.45%, whereas the PPV for TRS was 66.7% and the NPV was 83.3%. Pearson's correlation between TSI and histology was 0.561 ($P<0{,}001$) versus 0.556 ($P<0.001$) between TRS and histology.
Conclusions
TRS has higher accuracy and specificity when compared to TSI in the differential diagnosis of thyrotoxicosis. These results suggest that the differential diagnosis of thyrotoxicosis cannot rely initially or solely on TSI, as this approach may result in misdiagnosis. Our results lend support to the value of both TRS and TSI as the first step in differential diagnosis, owing to the fact that TRS may detect 7.1% of mild GD with negative TSI and TSI alone may leave 32.3% of patients misdiagnosed.

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P1049

Dependency between vitamin D3 and serum titers of the thyroid autoantibodies in smoking cigarettes patients with Graves' disease - one year follow-up - preliminary study

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Purpose
The aim of this study was to evaluate the association between the serum vitamin D level and changes in the titers of the anti-TSH receptor (TSHR), antithyroglobulin (Tg), and antiperoxidase (TPO) autoantibodies (Abs) in smoking cigarette Graves' disease (GD) patients, with and without the vitamin D supplementation.

Methods
The study was performed from January 2015 to December 2016. It consisted of 136 patients. The intensity of nicotinism was assessed based on the Fagerström Test for Nicotine Dependence. Serum vitamin D level and the titers of TSHR-Abs, TPO-Abs, and Tg-Abs were analyzed retrospectively. Studied parameters were analyzed at entry and 1, 6 and 12 months following baseline.
Results
The titers of TSHR-Abs were significantly higher at baseline in GD patients treated with vitamin D3 {D3(+)} than in patients not receiving vitamin D3 {D3(−)} (8.9 vs 0.7 IU/ml, $P<0.001$); at the remaining time points, no statistically significant differences were noted. Among the GD D3(−) patients, the titers of TSHR-Abs were statistically significantly lower at baseline (Me: 0.7 IU/ml) than for each subsequent time of point (Me: 7.8, 6.6, 6.2 IU/ml; $P<0.05$). In the group of GD D3(+) patients, the titers of TSHR-Abs at baseline were comparable to the level after 1 (Me: 8.9 vs 18.5 IU/ml, $P=$NS) and 12 months (Me: 6.1 IU/ml, $P=$NS) of follow-up. There was a significant difference between 1 and 6 (Me: 18.5 vs 11.8 IU/ml, $P<0.001$), 6 and 12 months (Me: 11.8 vs 6.1, $P<0.001$) of observation. The titers of TPO-Abs at baseline in the GD D3(+) patients were significantly higher than in GD D3(−) patients (290 vs 38 IU/ml, $P<0.001$). At all subsequent time points, we noticed no significant difference. In the GD D3(+) patients, the titers of Tg-Abs at baseline were significantly higher than in GD D3(-) patients (97 vs 24 IU/mL, $P=0.002$). At all subsequent time points, there were statistically significantly smaller differences after one month (243 vs 92 IU/ml, $P=0.03$), and after 6 (220 vs 104 IU/ml, $P=0.009$), and 12 months (200 vs 52 IU/ml, $P=0.001$) of the follow-up.
Conclusion
In almost all cases, we observed that vitamin D does not have a strong association with the titers of thyroid autantibodies. Nicotine does not allow the reduction of the titers of TSHR-Abs in GD patients supplemented with vitamin D3.

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P1050

Visual evoked potentials in the diagnosis of orbitopathy during the course of Graves' disease

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Graves' disease (GD) is an autoimmunological disorder leading most often to hyperthyroidism and invasive-edema ophthalmopathy (Graves ophthalmopathy – GO).
Aim
Estimation of visual evoked potentials (VEP) results with the indicators of activity and advancement of the progress of GO.
Materials and methods
The examined group consisted of 100 patients between the ages of 31 and 77, hospitalized in the Department of Endocrinology and Metabolism. The duration of GD from the first clinical signs to the start of treatment was between 3 months to 20 years. Changes in the eye due to GO occurred from 3 months to 6 years. VEPs were carried out according to the recommendations of the International Federation of Clinical Neurophysiology. Latencies and amplitudes of VEP components were compared to normal values in a group of 30 healthy person without an autoimmunological thyroid disorder.
Results
According to the NOSPECS scale, 9 patients showed no visual symptoms. In 17 cases, class 1 or 2 was diagnosed. Furthermore, in 74 patients classes between 3 and 6 were observed. A possible loss of vision due to the visual nerve damage (class 6) was found only in 4 patients. The CAS criteria in 8 patients were equal to 0, and in the remaining 14 patients from 1 to 3. Active GO was diagnosed in 47 patients. In 74 patients, abnormal VEPs were recorded. Normal parameters of VEP were observed only in 26 patients. These were patients with inactive or mild processes involving eye balls. Changes in the latency of P100 increased from 125 ms in mild to 127 ms in intermediate and 129 ms in intense GO. Referring to the control group, a statistical change was observed in the latency of P100 and N145. It was prolonged already in the mild occurrence of GO which confirmed subclinical visual nerve involvement.
Conclusions
VEP can be helpful in the diagnosing of visual nerve neuropathy in patients with GD. The clinical interpretation of changes of P100 and N145 latency is very important in patients with GO.

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P1051

Thyroid ultrasound alterations occurrence in patients with previous negative examination: A 6-years observational follow-up trial

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Background
Thyroid nodules represent a common clinical finding and their prevalence is increasing worldwide. However, the most recent international guidelines do not give indications on the need to retest adults with previous negative neck ultrasound (US).
Aim
To evaluate the incidence of thyroid US abnormalities in patients with previous negative thyroid US and identify patient's characteristics able to predict the risk of developing thyroid disease.
Methods
In 2011, 291 subjects were enrolled in a prospective clinical trial conducted in the Endocrine Unit of Modena to detect the prevalence of thyroid disease in adults unaware of thyroid pathology. Among these, 136 patients did not shown any US thyroid alteration. Up to now, 99 of these patients (61 females and 38 males, mean age 51 ± 12 years) were prospectively examined with thyroid US after six years with the same US device. Each patient was further clinically evaluated, updating anamnesis, physical examination and anthropometric measurements.
Results
During a mean interval between the first and the second US evaluation of 72.4 ± 6 months, 51 subjects (51.5%) developed thyroid US alterations, specifically 46 (46.5%) subjects developed thyroid nodules and 5 (5%) a US pattern of thyroiditis. According to the American Thyroid Association nodular sonographic pattern classification, among patients with nodular pathology we have found 26 subjects (56.5%) with at least one benign or very low-suspicion nodule, 9 (19.5%) with at least one low-suspicion nodule and 11 (24%) with at least one intermediate or high suspicion nodule. The incidence of US thyroid alterations is not significantly different among subjects with (49%) or without (51%) family history positive for thyroid disease ($P=0.366$). Moreover, thyroid abnormalities occurrence was not predicted by smoking habit ($P=0.615$), age ($P=0.826$), weight ($P=0.960$), BMI ($P=0.546$) and thyroid volume ($P=0.114$). These results were confirmed considering males and females separately.
Conclusions
These preliminary data show that more than 50% of patients have developed US abnormalities in a mean period of 6 years. Interestingly, among patients with thyroid nodular pathology, 24% of subjects have developed at least one intermediate or high suspicion sonographic thyroid nodule. This result justifies the need to retest patients, even when no US alterations have been detected during first examination. Currently, we are not able to predict thyroid alterations occurrence, since positive family history for thyroid disease, smoking habit, age, weight, BMI and thyroid volume seem to be not related to the incidence of US abnormalities.

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P1052

Evaluation of 32 patients with subacute thyroiditis

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Aim
Thyrotoxicosis is a clinical status related to increased thyroid hormones. It is caused by either hyperfunctioning thyroid tissue or destruction of thyroid. Subacute thyroiditis, also known as De Quervain or granulomatous thyroiditis, is an acute inflammatory disease of thyroid causing thyrotoxicosis. Clinical and laboratory features vary according to the course of disease. In this study, we

aimed to study clinical and laboratory features of the patients who were referred from internal medicine outpatient clinics to endocrinology department due to thyrotoxicosis.
Methods
We retrospectively evaluated electronic data of 32 patients who were followed-up by endocrinologists due to subacute thyroiditis in 2013–2018. Thyroid function tests, presence of antibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), onset of disease, achievement of euthyroidism, department of initial admission, and thyroid scintigraphy results where available.
Results
Twenty six (81.2%) patients were female. Twelve patients (37.5%) first attended to ear-nose-throat department, 8 (25%) to family medicine practitioner, 6 (18.8%) to internal medicine specialist, and 6 (18%) to general surgery departments due to complaints. Eight (25%) were attended to the outpatient clinics in spring, 7 (21.9%) in summer, 12 (37.5%) fall, and 5 (15.6%) in winter. Mean age was 42.9 ± 9.1 (33–69). Four patients' sera (12.5%) were positive for anti thyroglobulin antibody. Mean TSH level was 0.015 ± 0.024 μIU/ml (0.35–4.94), free T4 level 2.17 ± 0.77 ng/dl (0.7–1.48), free T3 level 5.74 ± 2.53 ng/dl (1.71–3.71), ESR 73.3 ± 17.3 mm/h (0–20), and CRP 55.5 ± 37.3 mg/l (0–8). Nineteen patients had scintigraphy. All yielded suppressed uptake in thyroid bed. Two (6.3%) patients developed permanent hypothyroidisim. Mean time lapse till achieving euthyroidism was 3.8 ± 2.9 months in 29 patients.
Discussion
Subacute thyroiditis must be kept in mind in differential diagnosis of thyrotoxicosis for correct diagnosis ve management.

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P1053

Cryoablation of goiter irrespective of thyroid profile

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Introduction
Thyroid nodules are extremely common. By age 60, about one-half of all people have a thyroid nodule. Cryoablation is used in a variety of clinical applications, using hollow needles (cryoprobes). Cryoprobes are inserted into or placed adjacent to diseased tissue which is desired to be ablated.
Objectives
To evaluate the effect of Cryoablation on the size & function of thyroid nodule, which may replace the need for surgery or radiotherapy.
Patients and methods
This is an interventional therapeutic study, conducted in Ain-Shams University hospitals; endocrinology clinic. Our study sample included 80 subjects, age between 20 & 60, having thyroid nodule diagnosed by ultrasound. Subjects were divided into 2 groups: Group 1 included 40 subjects 'control group' who were not subjected to cryoablation. Group 2 included 40 subjects 'cases' upon which cryoablation was done. Neck ultrasound were done for subjects & they were sampled for their TSH, free T4 & free T3 levels at start and after 3 & 6 months.
Results
There was high statistical significant difference between group 1 & group 2 regarding nodule size, after 6 months. Group 1 showed median nodule size after 6 months (0.85 cm) (IQR: 0.7–1.05)while cases showed (0.6 cm) (IQR: 0.3–0.9) (*P*-value 0.001). Females are more liable than males, to show nodule size reduction.
Conclusions
Cryoablation causes nodule size reduction, especially after 2nd session. Cryoablation does not affect thyroid function tests, all through our study.

Keywords: Cryotherapy, Thyroid nodule, Size reduction, TSH variation.
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P1054

Prevalence and clinico-epidemiology of hypothyroidism in Indian patients with type-2 diabetes mellitus and hypertension

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Introduction
Among the most common chronic non-communicable diseases in India, Type-2 Diabetes mellitus (T2DM) and hypertension (HT) are increasingly becoming a matter of public health importance. Hypothyroidism is also believed to be a common health issue in India, with one out of 10 people in the country diagnosed with the condition. Hence the objective of this cross-sectional, clinico-epidemiological, Pan-India study was to evaluate the prevalence of hypothyroidism in patients with T2DM or HT or both T2DM and HT and to understand the management practices in Indian real-world setting.
Methods
Adults (≥18 years) with a diagnosis of T2DM or HT or both (established or newly diagnosed), visiting physician for routine check-up, were enrolled in this study. Overt hypothyroidism was defined as TSH >4.50 μIU/ml (FT4: <0.8 ng/dl; FT3: <1.4 pg/ml); subclinical hypothyroidism (SCH) as TSH >4.50 μIU/ml (FT4: 0.8–1.8 ng/dl; FT3: 1.4–4.4 pg/ml). Descriptive statistics was used for statistical analysis.
Results
A total of 1501 (99.5%) patients completed the study (T2DM:500 [99.2%]; HT:499 [99.6%]; both T2DM and HT: 502 [99.8%]). Mean (±S.D.) age of the population was 52.9 ± 12.49 years. In patients with known case of hypothyroidism, 86 (17.1%), 111 (22.2%), and 87 (17.3%) patients had history of T2DM, HT and both T2DM and HT, respectively. In patients with T2DM, the newly diagnosed cases of hypothyroidism were 38 (7.6%; SCH: 5.2%) versus 86 (17.2%) previously diagnosed cases. In patients with HT, newly diagnosed cases of hypothyroidism were 58 (11.6%; SCH: 8.2%) versus 109 (21.8%) old cases. Among patients with T2DM and HT, the newly diagnosed cases of hypothyroidism were 58 (11.6%; SCH: 6.4%) versus 87 (17.3%) previously diagnosed cases. Overall prevalence of hypothyroidism in T2DM ($n = 1002$) and HT ($n = 1001$) was 26.85% and 31.17% respectively. In T2DM patients with newly diagnosed SCH, 16 (61.5%) patients were prescribed with thyroxine. In HT patients with newly diagnosed SCH, 25 (61.0%) patients were prescribed with thyroxine. In patients with T2DM and HT, newly diagnosed with SCH, 20 (62.5%) patients were prescribed with thyroxine. Most commonly prescribed dose of thyroxine was 25 μg for SCH in all cohorts.
Conclusion
We conclude that screening for thyroid disease among patients with T2DM and HT should be routinely performed considering the prevalence of newly diagnosed cases in the study. This study thus emphasizes on the extent of overlap between these diseases and highlights the need for early diagnosis for effective management/better outcome.

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P1055

Pos-thyroidectomy hypoparathyroidism: The role and timing of calcium determination

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Introduction
Postoperative hypocalcemia is among the most frequent morbidities after total thyroidectomy. Although most postoperative hypocalcemia is temporary, it causes prolonged hospitalization and a decrease in quality of life. For all this, early diagnosis is essential to start treatment as soon as possible. In this study, we determined whether early serum calcium levels can predict the development hipoparathyroidism.
Methods
A total of 122 patients underwent total thyroidectomy with or without neck dissection between 2016 and 2017 were reviewed. Total calcium levels were evaluated at 6 h, 1 day an 1 month postoperatively. Serial serum calcium measurements were recorded as well as details of the operation, pathology, demographic and clinical data. To assess the value of the most appropriate test for the diagnosis of hypoparathyroidism, the sensitivity and specificity of calcium at 6 and at 24 h was studied and the area under the receiver operating characteristic (ROC) curve (AUC) was used to measure the relative predictability of these variables or criteria.
Results
63.9% patients did not develop hypocalcaemia but 29.5% were found to have temporary hypocalcaemia and 6.6% had permanent hypocalcaemia. No differences were observed for sex, age, neck dissection types and pathology between normocalcemic and hypocalcemic patients. The average calcium was 8.4 mg/dl at 6 h and 8.05 at 1 day postoperatively ($P < 0.05$). For the diagnosis of transient hypocalcemia, AUC from 6 and 24 h calcium levels was 0.724 and 0.963 respectively ($P < 0.001$). The threshold of 7.75 mg/dl was obtained by means of the ROC curve analysis, with 98% of sensitivity and 66% specifity from 6 h calcium, and 8 mg/dl with 89% of sensitivity and 68% specifity from 1 day postquirurgical calcium. However for the diagnosis of permanent hypocalcemia, AUC from 6 and 24 h calcium levels was 0.797 and 0.691 respectively

($P<0.001$) and the calculated threshold of 7.45 mg/dl (94% sensitivity and 75% especifity) from 6 h calcium and 6.95 mg/dl (93% sensitivity and 87% specificity) from 1 day postquirurgical calcium.
Conclusion
Post-thyroidectomy hypocalcemia is a common complication of total thyroidectomy. Our results suggest that the calcium levels on day 1 postoperatively are useful in predicting the development of hypocalcemia and the hypoparathyroidism diagnosis.

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P1056

Adaptation and cross-cultural validation of the Spanish version of the Thyroid-Related Quality-of-Life Patient-Reported Outcome (ThyPRO) questionnaire

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Introduction
The thyroid-related quality-of-life patient-reported outcome ThyPRO questionnaire is the most widely used tool for measuring health-related quality of life (QoL) in patients with benign thyroid diseases. The aim of this study was to adapt and validate a Spanish version of the ThyPRO.
Methods
The ThyPRO consists of 85 items, grouped in 13 scales and one single QoL item. Scales cover physical and mental symptoms, well-being and function, social and daily function, cosmetic concerns and overall QoL-impact. ThyPRO39 is a short version of the ThyPRO consisting of 39 items grouped in 11 scales and one single item. The Spanish version of the ThyPRO was developed using the forward-backwards translation: 1) forward translation from English to Spanish by two independent native Spanish translators; 2) reconciliation of both versions in a preliminary consensus-translated draft; 3) back-translation by an English native translator not familiar with the original version of the questionnaire; 4) comparison and discussion of the back-translated version and the master English questionnaire; 5) preparation of a new draft translation containing appropriate changes; 6) second back-translation by a different English native translator; 7) discussion of the second back-translation and approval of the final Spanish draft. The translation was pretested on five representative individuals with different thyroid diseases, by cognitive interviewing. The definitive questionnaire (ThyPROes) was completed by 155 patients with benign thyroid diseases attending the Endocrinology Department in a single hospital in Spain. Equivalence between the Spanish version and original (Danish) questionnaire was assessed using tests for differential item functioning (DIF) by means of ordinal logistic regression, controlling for specific diagnosis. The independent variables were language group and scale score, and an interaction term scale score*language group. Non-uniform DIF was considered when the interaction term was significant. DIF magnitude was considered substantial if it could explain more than 2% of the variance in the item score (R^2 difference >0.02).
Results
Eight items were flagged with DIF in the ThyProes (one with non-uniform DIF) and two items in the ThyPro39es. Eight scales of ThyPROes and nine scales of ThyPRO39es were free of DIF. The magnitude of DIF was small in most of cases (explained variance in the item score $<3\%$ in seven items of ThyProes and in one of ThyPro39es), with probably minor impact in scales scores.
Conclusion
The presented Spanish versions of the ThyPRO and the ThyPRO39 show a good cross-lingual validity and are suitable for use in clinical studies.

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P1057

Antithyroid drugs can be associated with increased frequency of antibodies against type 2 5'-deiodinase enzyme influencing their therapeutical effectiveness in hyperthyroid Graves' ophthalmopathy

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Antithyroid drugs represent mainly the first choice therapy in hyperthyroid Graves' disease. Their therapeutical ineffectiveness can lead to the onset or the severity of ophthalmopathy associated with Graves' disease. Type 2 5'-deiodinase enzyme (DIO2) plays a crucial role besides type 1 5'-deiodinase enzyme in the development of Graves' hyperthyroidism. Anti-thyroid drugs inhibit the activity of both type 5'-deiodinases blocking the synthesis of thyroid hormones and can induce antineutrophil cytoplasmic antibodies. In this study, the frequency of antibodies against type 2 5'-deiodinase and their effects on the inhibition of thyroid hormone synthesis were investigated during antithyroid drug therapy. Antibodies against DIO2 peptides (cys- and hom-peptides) were studied in 78 patients with Graves' disease (58 females and 20 males, mean age of 43 ± 14 years, 39 had ophthalmopathy) and 30 healthy controls (27 females and 3 males, mean age of 47 ± 16 years) using ELISA. The thyroid hormone and antibody serum levels were measured with chemiluminescence immuno-assay and ELISA. In hyperthyroid patients treated by propylthiouracil (PTU), a greater frequency of antibodies against DIO2 peptides was demonstrated compared with those treated by methi-ma-zole (MMI) (3/3 vs 5/23 cases, $P<0.002$ for cys-peptide and 2/3 vs 2/23 cases, $P<0.027$ for hom-peptide antibodies). The patients, who were treated with PTU and had cys-peptide anti-body positivity, demonstrated significantly increased TSH receptor antibody levels compared with those treated with MMI (26.4 ± 10.57 vs 6.96 ± 4.85 IU/l, $P<0.011$). In hyperthyroid Graves' ophthalmopathy, the patients were hom-peptide (0/12 vs 3/11, $P<0.05$) and cys-peptide (0/12 vs 5/12, $P<0.012$) antibody negative after MMI therapy in comparison with patients without ophthalmopathy. In hyperthyroid Graves' ophthalmopathy, the occurrence of hom-peptide antibodies was associated with elevated FT_4 (3.08 ± 0.86 vs 2.02 ± 0.49 ng/dl, $P<0.013$) and FT_3 (10.44 ± 6.02 vs 5.36 ± 1.42 pg/ml, $P<0.003$) serum levels compared with those who were antibody negative. In summary, an increased presence of antibodies againts DIO2 peptides could be demonstrated after PTU therapy in hyperthyroid Graves' disease. None of hyperthyroid cases with ophthalmopathy had antibodies against DIO2 peptides after MMI therapy. The presence of DIO2 peptide antibodies was associated with a prolonged hyper-thyroidism and increased TSH receptor antibody levels declining the therapeutical effective-ness of antithyroid drugs.

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P1058

The thyroid gland in acromegaly

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Objective
Acromegaly is frequently associated with thyroid diseases. In this study we evaluated the incidence, morphology of the thyroid and the influence of surgery, iradiation and medical therapy used in acromegaly on thyroid function.
Methods
We evaluated 20 patients diagnosed with acromegaly using thyroid ultrasonography and measurement of IGF1, GH, TSH, free T4. 65% of the patients had active disease and were under medical therapy.
Results
35% of the patients had multinodular goitre assesed by thyroid ultrasonography, one patient was diagnosed with papillary thyroid carcinoma and another with medullary thyroid carcinoma. 20% had autoimmune chronic thyroiditis with hypothyroidism. We did not find a relation between the duration of the disease and nodular goitre. After one year of treatment with ocreotide or lanreotide there was a reduction in the thyroid volume ($P=0.05$). The majority of patients (30%) had indication for surgical treatment based on the ultrasonographic characteristics of the goitre.
Conclusions
Goitre is a common finding in acromegaly. In our study, diffuse goitre appeared in the early course of the disease. Nodul formation, enlargement of the thyroid gland may occur independent of TSH. Long-term stimulation by GH can be responsable for the thyroid enlargement.

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P1059

Metabolic profile in patients with subclinical hypothyroidism

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Background
Thyroid function regulates a wide array of metabolic parameters and significantly affects lipoprotein metabolism. Subclinical hypothyroidism (SCH) is the most common thyroid disorder, with a prevalence up to 10% in adult populations. Subclinical hypothyroidism is defined as mild elevation in thyroid stimulating hormones (TSH) in presence of normal free thyroxine (fT4) and free triiodothyronine (fT3). This mild elevation of serum TSH is caused by a minor initial decrease in thyroidal secretion of thyroxine (T4) which activates piruitary-thyroid axis. The reason for maintaining T4 values within the reference range is the exquisite sensitivity of the pituitary thyrotroph for even very small decreases of serum T4.
Objectives
The aim of this study was to compare metabolic profile in patients with SCH and healthy controls.
Methods
The study group consisted of 75 patients with SCH (group 1, TSH 4.6–24.49 mIU/L) and 47 healthy controls (group 2, TSH 0.4–4.2 mIU/L) who were matched by age and weight. We compared glucose, HbA1c, HOMA index, cholesterol, HDL, LDL and trigyceride levels between groups. The data were analyzed by Welch Two Sample *T*-test with 95 percent confidence interval.
Results
There were no statisticaly significant difference in glucose levels, as well as in HbA1c and HOMA index between groups (glucose 5.249 vs 5.198 mmol/l; $P=0.725$; HbA1c: 5.55% vs 5.42%; $P=0.126$; HOMA 2.51 vs 2.48; $P=0.959$). Also, there were no statisticaly significant difference in cholesterol levels, HDL, LDL and trigyceride levels between groups (cholesterol 5.527 vs 5.563 mmol/l; $P=0.872$; HDL 1.522 vs 1.579 mmol/l; $P=0.411$; LDL 3.407 vs 3.414 mmol/l; $P=0.968$; Tg 1.317 vs 1.194 mmol/l; $P=0.34$).
Conclusions
These data suggest that activation of pituitary-thyroid axis and increase of TSH levels does not affect metabolic profile in patients with subclinical hypothyroidism.

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P1060

The efficacy of intrathyroid injected steroids for painful lymphocytic thyroiditis

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Thyroidal pain is usually due to subacute thyroiditis. It seldom occurs in patients with Hashimoto's thyroiditis (HT), and then its name is painful HT (PHT). Differently from subacute thyroiditis, occasional PHT patients show no benefit from medical treatment so that thyroidectomy is frequently needed. We report two women diagnosed of PTH and successfully treated with intrathyroidal corticosteroid injection after initial unsuccessful treatment with L-thyroxine replacement and oral corticosteroids.
Case 1
A 36-year-old woman presented in January 2015 with a 9-month history of episodic pain on the anterior neck and otalgia. Physical examination showed diffusely enlargement of both thyroid lobes with a firm consistency and marked tenderness in right lobe. Thyroid function tests revealed subclinical autoimmune hypothyroidism (TSH 6.57; FT4 12.0 pmol/l, AcTPO > 600 UI/l). Thyroid ultrasound (US) revealed a diffusely enlarged thyroid gland with heterogeneously hypoechoic pattern involving the entire area of both lobes. She received a short course of prednisone without relief, and substitutive thyroxine was started, with initial improvement and greater interval between episodes. Two years later, euthyroid (TSH: 1.23) pain flared-up, and intrathyroid corticosteroid injection was proposed. US-guided injection of 40 mg of triamcinolone was performed in both lobes aimed to the areas of hypoechogenicity. After treatment, the patient experienced almost total relief of pain and tenderness, and thyroid became less consistent at palpation.
Case 2
A 47-year-old woman, consulted on December 2016 because of 6-month thyroidal pain. Before the pain appeared, she was taken levothyroxine for 8 years because autoimmune hypothyroidism, with normal TSH. Pain had been attributed to subacute thyroiditis, although she had normal sedimentation rate and lymphocytic infiltration on FNAC, and was treated with oral corticosteroids (up to 45 mg of prednisone) and NSAIDs without success. Thyroid ultrasonography revealed marked hypoechogenity and high vascularization on Doppler exam. Intrathyroidal corticosteroids were proposed. US-guided injection of 40 mg of triamcinolone throughout the gland was performed. After first injection, pain was relieved, with residual tenderness. As she had residual discomfort that limited her to speak loudly, treatment was repeated at six and eleven months improving with every injection. After last injection the pain relief was complete.
Conclusion
US-guided intrathyroidal injection of corticosteroids can be an effective to treat painful HT. This technique can avoid surgery to treat this rare presentation of Hashimoto's thyroiditis.

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P1061

The peripheral blood and thyroid compartment in patients with Graves' disease: helper and regulatory T-cells and decreased B-lymphocytes

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Graves' disease (GD) has been recognised for more than 100 years, its pathophysiological mechanisms are incompletely understood.
Aim
To investigate the helper- (Th-cells) and regulatory T-cells (Treg) influence on B-lymphocytes phenotypic composition of blood and thyroid tissue in GD.
Materials and methods
The study included 43 women with GD, mean age 39.95 ± 14.38, who were performed the epifascial thyroidectomy and 67 healthy women were examined as a control. The median of thyroid stimulating hormone, autoantibodies to TSH receptor, free thyroxine and triiodothyronine level was respectively 0.08 (0.01; 0.58 mIU/l, 10.25 (6.85; 24.68) IU/ml, 16.89 (11.39; 31.5) and 5.93 (4.6; 7.7) nmol/ml. Phenotypic composition of Th-cells, Treg and B-lymphocytes were measured by flow cytometry, using direct immunofluorescence, respectively, of whole peripheral blood and lymphocytes isolated from thyroid tissue.
Results
In patients with GD in peripheral blood increased the level of B1-cells. In thyroid tissue of GD patients we observed high level of memory B-cells, but decreasing the relative number of B1-cells, in contrast to its level in peripheral blood ($P<0.001$). In healthy control increasing the content of activated B-lymphocytes in the blood accompanied by a co-directional reaction from Treg, but in patients with GD such mechanism is disrupted. In peripheral blood of GD patients we revealed the positively interaction between the relative amount of B-lymphocytes with Treg and activated T-helper cells ($r=+0.39$, $P=0.009$), B2-cells and naïve B-lymphocytes with $CD3^+CD4^+CD25^+$- ($r=+0.49$, $P<0.001$ and $r=+0.42$, $P=0.003$, respectively) and $CD3^+CD4^+CD127^{Low}CD25^{High}$-cells ($r=+0.49$, $P<0.001$ and $r=0.37$, $P=0.012$, respectively). In thyroid tissue of GD patients the relative number of $CD3^+CD4^+$-cells interact with the level of $CD19^+CD5^+CD23^+$-lymphocytes ($r=+0.79$, $P=0.036$) and the percentage number of $CD3^+CD4^+CD25^+$-cells with $CD19^+CD23^+$- ($r=+0.85$,$P=0.014$), $CD19^+CD5^-CD23^+$- ($r=0.80$,$P=0.034$), $CD19^+CD5^+CD23^+$- ($r=+0.93$, $P=0.025$) and $CD19^+CD27^+CD23^+$-lymphocytes ($r=+0.82$, $P=0.023$).
Conclusion
It is assumed that in patients with GD and thyrotoxicosis decreased not only the content of Treg in peripheral blood, but also a violation of their functional activity. In patients with GD the ac ivated B lymphocytes and Treg does not involve in correlation system, respectively, in peripheral blood and thyroid tissue.

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P1062

Influence on remission rates of hyperthyroid periods during anti-thyroid drug therapy of Graves' disease: retrospective study of $N=301$ patients

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Introduction and aims
Thionamide may have immunosuppressive mechanisms. However, data suggest restoration of the immunological regulation as patients return to the euthyroid state may better explain remission, How successfully patients are kept euthyroid during a course of antithyroid drug therapy for Graves' hyperthyroidism, and whether not continuously maintaining normal thyroid function is associated with a worse prognosis, is not known.
Aims
1) assessment of duration of euthyroid, subclinical and overt hyperthyroid periods during thionamide therapy of newly diagnosed Graves' disease, 2) thyroid function with shorter (2–4 weeks) compared to longer (5–6 and >7 weeks, respectively) intervals between out-patient visits, and 3) whether periods of hyperthyroidism are associated with lower remission rates.
Methods
Retrospective anaylsis of $N=301$ patients treated with thionamides for ≥ 10 months at a single thyroid out-patient unit from 2010 to 2015, patients in remission ($N=156$) compared to those with relapsing hyperthyroidism ($N=145$) – median follow-up after stopping thionamides 20 and 14 months, respectively. Multivariant regression analysis including length of different thyriod functions, scheduled intervals between visits, and other factors such as age, TRAb, degree of hyperthyroidism at first diagnosis, time to normalization of fT4 after initiation of antityhroid drug therapy, or smoking status to define independent predictors of remission.
Results
Median treatment duration (15.0 vs. 15.6 months) was comparable ($P=$n.s.). Relapsing patients displayed longer ($P<0.0001$ and $p<0.05$, respectively) periods of overt (11 ± 3.5 vs. 2.6 ± 3.3 weeks) and subclinical (10.4 ± 2.3 vs. 8.3 ± 4.2 weeks) hyperthyroidism, and shorter ($P<0.0001$) periods with normal thyroid function (33.9 ± 12.4 vs. 46.8 ± 12.1 weeks). Scheduled intervals differed widely within patients (2 to >7 weeks), were not different between groups, and did not influence thyroid function. Normal thyroid function at $>50\%$ of all visits was observed more frequently (92.3 vs. 64.1%) and at $\leq 5\%$ and 6–20% of all visits less ($P<0.0001$, respectively) frequently (0% and 0% vs 3.4 and 4.8%, respectivley) in remitting patients than in those who relapsed. Overt hyperthyroid and euthyroid periods were independent (opposing) predictors of remission, respectively, as were age, TSHR-Ab, fT4 at first visit, and time to first normalization of thyroid function.
Conclusion
Continuously maintaining normal thyroid function during antithyroid drug therapy may be associated with increased remission, whereas overt hyperthyroid periods with higher relapse rates. Intervals between visits >7 weeks were not associated with unfavourable outcome and identified, on an individual patient's basis, more often with patients in remission.

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P1063

The accuracy of diagnostic tests in amiodarone-induced thyrotoxicosis; a case-series

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Introduction
Amiodarone-induced thyrotoxicosis (AIT) can present a high morbi-mortality.Initial subtype identification facilitates appropriate management.We describe the utility of diagnostic tests in a cohort of patients with AIT.
Material and methods
Retrospective, observational study of 59 patients attended from 2007 to 2018 in outpatient clinic. Differential diagnosis: type I if FT4 and FT3 (TH) were normalized following therapy with antithyroid drugs (ATD)-methimazole alone or with potassium-perchlorate (*KClO4*); Type 2 if TH were reduced following oral prednisone (Pred) initiation and/or there was a hypothyroid phase following Pred discontinuation without prior AT; Mixed-AIT if patients needed both types of therapy to control TH. Most patients were initially treated with methimazole 30 mg daily unless diagnostic tests (thyroid scintigraphy and Doppler ultrasound) suggested type-2 AIT, where Pred was initiated. KClO4 (1 g/day 6–8 weeks) was associated when other medication was insufficient. Student's t test, χ^2 or non-parametric tests.
Results
Males 36 (61%). Mean age: 70 (SD12). Mixed-AIT: 44 (74%) patients, type 1-AIT: 9 (14%), five with prior subclinical hyperthyroidism. Type 2: 6 (10%) patients. Interleukin-6 levels elevated in 50%, 40% and 58% patients in type 1, type 2 and mixed AIT respectively ($P=0.7$ among groups). Thyroglobulin and/or thyroid-peroxidise antibodies raised in 11% with type 1, 16% with type 2, and 8% with mixed-AIT ($P=0.5$).Tc-99m-pertechnetate-thyroid scan: no uptake in 39/40(97%). Technetium-99m–sestamibi (Tc-MIBI) thyroid scintigraphy: uptake in 1/3 (33%) type-2 patients, 5/5 (100%) type-1 patients ($P=0.035$) and 23/27(85%) mixed-AIT patients ($P=0.3$) showed patchy, diffuse or localized uptake. Colour-Doppler ultrasound: absent vascularity in 2/5 (40%) type-2 patients, 1/7 (14%) type-1 patients, and 23/40 (57%) mixed-AIT patients ($P=0.35$). Initial FT3/FT4 ratio was higher in type I;median 0.2 (IQR:0.18–0.33) compared to type II, 0.14 (IQR:0.13–0.15) ($P<0.0001$) and to mixed-AIT:0.16 (IQR:0.12–0.19) ($P=0.007$). Optimal FT3/FT4 cut-off in *ROC-curve* to define those who required ATD (type I or mixed-AIT) vs. those only requiring Pred (type II-AIT) was 0.14;sensitivity: 0.65, specificity: 0.6. 17/53 (32%) patients with type I or mixed-AIT required *KClO4* to control TH,15/17 (88%) normalising TH with no severe adverse events. In 7/59 thyroidectomy was performed. One patient died from post-operative sepsis.
Conclusions
Diagnostic tests were of limited value for initial AIT classification, showing significant overlap. Initial FT3/FT4 ratio could potentially be useful for differential diagnosis. Response-to-therapy indicated mixed AIT was the most frequent form. KClO4 association was safe and effective in Type I and mixed forms.

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P1064

Arterial stiffness in hyperthyroid patients is deteriorated due to thyroid hormones

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Aim
It is aimed to evaluate whether arterial stiffness, which is an independent risk indicator for hyperthyroid cardiovascular diseases, is affected by pulse wave analysis (PWA) and to observe changes in patients treated with hyperthyroidism.
Methods
A total of 102 volunteers were included in the study (30 in the overt hyperthyroid group, 28 in the subclinical hyperthyroid group and 14 with euthyroidism by antithyroid therapy and 30 healthy). The arterial stiffness measurements of the subjects participating in the study were performed with the PWA device, which measures the sleeve-based oscillometric measurement of the brachial artery.
Results
Systolic blood pressure, pulse rate, central systolic blood pressure, cardiac output, augmentation index and PWV measurements were significantly higher in the hyperthyroid group than in the control group. The heart rate and PWV in the subclinical hyperthyroid group was significantly higher than the control group. In the euthyroid group, systolic blood pressure, central systolic blood pressure, cardiac output, cardiac index and PWV were found significantly higher than the control group. There was also a negative correlation between Aix@75 and TSH, and a positive correlation between Aix@75 and free thyroid hormones.
Conclusion
In our study, we observed that arterial stiffness was adversely affected by an overt or subclinical increase in thyroid hormones and this correlated with thyroid hormones. We recommend that PWV measurement, which is a simple method for detecting CVD risk, can be used in these patients.

Keywords: Arterial stiffness, augmentation index, hyperthyroidism, pulse wave analysis
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P1065

Gestational and postpartum complications in women with chronic autoimmune thyroiditis receiving iodine and selenium therapy

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Introduction
Iodine may aggravate maternal autoimmune thyroid diseases during and after pregnancy, but selenium could defend against it's harmful effect. Objective: to study the course and complications of Hashimoto's thyroiditis in pregnant and lactating women receiving iodine and selenium therapy. Material and method. Serum TSH, free-T4 and anti-thyroid peroxidase-antibody were measured in 30 women with chronic autoimmune thyroiditis in every gestational trimester, on the 6th-7th postpartum week and at 6–9 months after delivery. They received 100 mcg/day selenium and 100–200 μg/day iodine ± L-thyroxine during the studied period. The results were compared to those of 30 women without chronic autoimmune thyroiditis, receiving 100–200 μg/day iodine ± L-thyroxine during pregnancy and lactation.
Results
In the thyroiditis group nine women were known with thyroid disease before pregnancy, and hypothyroidism developed in other 20 cases during pregnancy (27 hypothyroidism and two isolated hypothyroxinaemia). Thyroid function has not normalized yet in any of these cases. One imminent abortion and one imminent preterm delivery were noticed. In the postpartum period two cases of postpartum thyrotoxicosis with autolimited course and two cases of severe hypothyroidism developed. In women without chronic autoimmune thyroiditis no gestational or postpartum complications, no postpartum thyrotoxicosis appeared. In the second group nine cases of isolated hypothyroxinaemia were recorded, their proportion being mildly higher, at the limit of significance compared to the thyroiditis group ($P = 0.04$). Conclusions. Hypothyroidism developed frequently among pregnant women with Hashimoto's thyroiditis receiving iodine with selenium, but gestational and postpartum complications were not observed significantly more frequently in these women compared to those without chronic autoimmune thyroiditis.

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P1066

The effects of exenatide treatment on thyroid

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Glucagon-like peptide-1 (GLP-1) is an increatin hormon with various glucoregulatory effects, and exenatide is a GLP-1 receptor agonist used in the management of type 2 diabetes mellitus. C cell hypertrophy was seen in animals treated with GLP-1 receptor agonists, but the effects of GLP-1 agonists on C-cell proliferation or neoplasia in humans have not been documented formerly. The aim of this study was to evaluate the impact of exenatide on structural and functional features of the thyroid in patients with T2DM treated with exenatide. Fourty-eight patients with T2DM were included in the study. 5 μg exenatide was started to all patients twice daily.After 4 weeks the dose was increased to 10 μg twice daily.Four patients who had severe vomiting were excluded. Serum free triiodothyronine (T3), free thyroxine (T4), thyrotropin (TSH), anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg), carcino-embryonic antigen (CEA) and calcitonin were measured and thyroid ultrasonography was performed before the treatment was started and after 6th month. Fourty-one women and three men were included in the analysis with a mean age of 47.84 ± 7.37 years. The laboratory parameters and thyroid ultrasonographic features are summarized in the table. A significantly statistically decrease was achieved in TSH ($P < 0.001$) and thyroid volume (P:0.047). The statistical analysis was performed with 32 patients who were not using levothyroxine at the beginning, and TSH decrease was still statistically significant (P:0.022), whereas the reduction of the thyroid volume lost its significant difference (P:0.130). In conclusion, our study showed no difference in serum CEA and calcitonin level after 6 months of exenatide therapy, whereas a reduction in the thyroid volume was achieved for the first time in the literature .

Table 1 Demographic features and laboratory parameters at the beginning and after 6 months

	Before exenatide	6 months after exenatide	P
Weight	112.79 ± 14.73	102.98 ± 14.73	< 0.001
BMI	44.41 ± 6.63	40.18 ± 6.08	< 0.001
HbA1c	7.75 ± 1.24	6.74 ± 0.94	< 0.001
TSH	2.31 ± 1.09	1.85 ± 0.86	< 0.001
Free T4	0.88 ± 0.13	0.89 ± 0.09	0.888
Free T3	3.38 ± 0.45	3.50 ± 0.32	0.150
Anti TPO	64.88 ± 158.33	57.36 ± 141.79	0.072
Anti TG	11.57 ± 39.05	10.85 ± 37.37	0.120
CEA	1.89 ± 1.34	1.72 ± 1.03	0.193
Calcitonin	2.55 ± 1.13	2.55 ± 1.63	0.994
Thyroid volume	16.42 ± 15.59	14.95 ± 13.28	0.047

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P1067

Evaluation of anti-thyroglobulin antibodies in pregnant women in Area IV of Asturias

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Introduction
Hypothyroidism in pregnancy is a topic widely studied in recent years, especially in those women with positive autoimmunity. However, usually the only determination of antibodies that is made is the thyroid antiperoxidase antibodies (anti-TPO). In this study we wanted to know what incidence of anti-thyroglobulin antibodies (anti-Tg) our pregnant women present and what repercussion they can have on thyroid function.
Materials and methods
Anti-TPO and anti-Tg antibodies were analyzed in plasma of 147 consecutive women in her first trimester of pregnancy seen in the sanitary area of Oviedo in Asturias. Thyroid function was also evaluated, using the normal reference values for our area (TSH:0.2–4.5).
Results
Anti-TPO positive antibodies were detected in 14 (9.5%) of the 147 women and anti-Tg antibodies in 12 (8.2%) of them. In 87.07% of the patients none of the antibodies were detected, 4.76% had positive anti-TPO antibodies and negative anti-TG, and 3.40% presented positive anti-TG with negative anti-TPO. The thyroid function of these pregnant women according to their autoimmunity was as follow : In the case of patients with negative anti-TPO and positive anti-TG, 2 of 5 presented normal TSH, but in the range between 2.5 and 4.5, who would require treatment following 2017 ATA recommendations.
Conclusion
In our area, 12.92% of pregnant women have positive thyroid autoimmunity. Just 3.40% women presented only anti-Tg positive antibodies. Our patients with negative anti-TPO and positive anti-Tg antibodies had normal thyroid function, but 40% of them could require levothyroxine treatment. So we recommend the evaluation anti-Tg antibodies in those pregnant women who show negative anti-TPO antibodies.

TSH	AntiTPO - AntiTg -	AntiTPO + AntiTg -	AntiTPO − AntiTg +	AntiTPO + AntiTg +
0.01–0.2	5	0	0	0
0.2–4.5	115	7	5	3
4.5–10	8	0	0	1
> 10	0	0	0	3

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P1068

First extracervical (remote-access) thyroid lobectomy for large specimen without a visible scar via a transoral vestibular and retroauricular approach (TOVARA)

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Background
Both Transoral (TOETVA) and several Retroauricular approaches (e.g. EndoCATS) are described as feasible and safe procedures in the literature. The TOETVA enables angulation of instruments and provides a good working space by dividing the strap muscles in the first step. Therefor one should be able to dissect even larger specimen than the short incision in the lip allows to remove. However EndoCATS is a single port access with limited working space, but with good potential to increase incision length along the hairline without leaving a visible scar to remove large specimen.
Methods
In December 2017 a patient with a 65 ml nodule in the right thyroid lobe asked for an endoscopic resection without a visible scar in the décolleté. She rejected ABBA because of the areolar incisions. As EndoCATS has a limited working space, we decided to improve our technique by a combination with TOVARA which provides a better angulation and an increased working space.
Results
The operation was performed as planned in January 2018, by first dissecting the specimen with TOVARA and removing it via EndoCATS on the ipsilateral side. The operation time was 165 min. There were no complications except of a mild hypocalcemia on the first postoperative day. A numbness of 5 cm in diameter at the chin vanished within 14 days. The patient had a VAS for pain of 2 at the first day and 1 for the next 3 days. RLN and EBSLN were proven intact by laryngoscopy. Wound healing was primarily and without infection. The patient was highly satisfied with the procedure.
Conclusions
This is the first report about a hybrid operation of the two endoscopic techniques TOVARA and EndoCATS. Only extracervical endoscopic thyroid surgery provides the benefit of an unscathed décolleté. It is the next step in endoscopic thyroid surgery to combine safe techniques to enlarge the number of possible indications.

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P1069

Study of possible relation between thyroid volume, nodule formation and glucose metabolism disordersin egyptian population

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Insulin resistance (IR) with compensatory hyper-insulinemia are key factors involved in the pathogenesis of glucose metabolism disorders (including impaired fasting glucose and glucose tolerance and frank diabetes mellitus) as well as increased thyroid gland volume and nodule prev-alence in patients with metabolic syndrome. On the other hand, thyroid hormone contributes to the regulation of carbohydrates metabolism and pancreatic function. This cross-sectional study investigated the possible association between the different glucose metabolic disorders (GM) and thyroid gland volume. The study was conducted on 400 subjects over one year duration, divided into 50% diabetic patients in comparison to 25% pre-diabetics and 25% cross-matched control. All the subjects were investigated by fasting and postprandial blood sugar and fasting insulin level (for HOMA-IR calculation) as well as TSH assay combined with thyroid ultrasound. The results showed that thyroid volume was significantly larger in patients with diabetes com-pared to the control as well as significant positive correlation between thyroid volume and FBS, fasting insulin, HOMA-IR, 2-h pp BS and HbA1cin. Besides, there was significant association between serum TSH levels and thyroid volume. The main regulator of thyroid cell growth and differentiation is TSH. The elevated insulin levels due to IR lead to an increase in IGF-1 levels (which is an important hypertrophic and progression factor for a series of cell types including thy-roid cells with increased risk of malignancy in such patients).

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P1070

Final diagnosis of thyroid nodules classified as Bethesda-4 after Fine-needle aspiration

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Introduction
Fine-needle aspiration (FNA) is indicated in suspicious thyroid nodules or big ones. Bethesda system classifies them according to the cytological malignancy risk. Bethesda category 4 (B4) comprises follicular neoplasms and suspicious follicular neoplasms. *Aim*: Determine final diagnosis of B4 nodules and study associations between malignancy and other variables.
Methods
Retrospective study of patients with nodules classified as B4 after FNA in our hospital between 2013 and 2017. Statistical analysis: SPSS v.19.0 (Student's *t* test to compare means and χ^2/Fisher's test for proportions).
Results
141 patients, 73.8% women, mean age: 53.33 ± 14.90. 76.6% evaluated by the Endocrinology service prior to the FNA (21.3% previous thyroid pathology; 87.2% normal function). Symptoms: 88.7% asymptomatic. 5.7% cervical pain, 3.5% dysphonia, 3.5% dysphagia. Nodule discovery: 49.6% accidentally discovered in imaging studies done for other reasons, 35.5% palpation, 8.5% symptoms related to the nodule and 6.4% in routine follow-up sonography (US). Sonography characteristics: maximum diameter: 30.93 ± 16.88 mm. 82.3% solid, 56.7% hypoechoic, 30.5% hypervascular, 9.2% coarse calcifications, 4.3% suspicious adenopathies and 1.4% microcalcifications (In the US 9.9% suspicious, 11.3% non-suspicious, 78.8% undetermined). 20.5% of them with previous FNA (1.4% B2, 7.8% B1, 11.2% B3). 84.4% patients underwent surgery (39.5% total thyroidectomy), 114.54 ± 84.97 days after FNA. Final diagnosis: 77.3% benign (73.9% adenoma, 15.2% noninvasive follicular thyroid neoplasm with papillary-like nuclear features [NIFTP], 10.9% nodular goiter) and 22.7% malignant (51.9% follicular carcinoma, 40.7% papillary carcinoma, 7.4% medullary carcinoma). Most prevalent diagnosis after surgery: 33.6% folicular adenoma, 21.8% Hürthle adenoma, 11.8% NIFTP. Incidental microcarcinoma in 12.6% of interventions. Association with malignancy: Cervical pain (1.8 vs 20%, $P = 0.010$), bigger maximum diameter (15.88 ± 1.72 vs 18.27 ± 3.23 mm, $P = 0.009$). Tendency to association with malignancy: microcalcifications (0 vs 7.1%, $P = 0.068$), hypoechogenicity (65.3 vs 89.5%, $P = 0.076$).
Conclusions
1) Incidentally discovered nodules equals clinically discovered ones.
2) Prevalence of malignancy in nodules classified as B4 is similar to the one reported in previous publications.
3) There is a statistically significative association between malignancy and clinical finding (cervical pain) and sonographic findings (bigger nodule size), as previously reported in the literature.

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P1071

Thyroid autoantibodies and quality of life in patients with benign thyroid diseases

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Objective
Thyroid autoimmunity has been proposed as a risk factor for impaired health-related Quality of Life (HRQoL), depression and anxiety, though evidence is still limited. The aim of the current study is to assess the association of thyroid autoimmunity with quality of life in patients with benign thyroid disease.
Design
A cross-sectional study was implemented, that included consecutive patients with benign thyroid diseases who visited the outpatient clinics of the Department of Endocrinology, 'Hippokration' General Hospital, Thessaloniki, Greece, between September 2016 and June 2017. Patients were excluded if they had a thyroid cancer or if they were not able to communicate in Greek. The Greek, cross-cultural validated, version of ThyPRO questionnaire was used, as it comprises a reliable and validated instrument to measure thyroid-related quality of life. The 84 questions of ThyPRO are categorized in 13 scales that involve: goiter,

hypothyroidism, hyperthyroidism and eyes symptoms, tiredness, cognitive impairment, anxiety, depressivity, emotional susceptibility, cosmetic complaints and impaired social, daily and sex life. The scales were all scored and the final scores were transformed to a scale from 0 to 100. Lower scores reflect a better thyroid-related quality of life, whereas higher scores reflect a worse quality of life. Thyroid hormones were measured and thyroid autoimmunity was assessed in all patients while their thyroid disease history was also recorded. IBM SPSS was used for Statistical Analysis.
Results
Two hundred and three ($n=203$) consecutive patients (183 women and 20 men) with benign thyroid diseases were included in the study. Of them, 81 patients (39.9%) had Hashimoto thyroiditis. When compared with patients with benign thyroid diseases but no thyroid autoimmunity, patients with Hashimoto thyroiditis had surprisingly lower scores in the impaired sexual life scale ($26.6\pm3\%$ vs $34.8\pm3\%$ respectively, $P=0.05$) but no difference in all other scales.
Conclusions
The current study did not demonstrate significant differences between patients with Hashimoto thyroiditis and patients with other benign thyroid diseases in regard to patient-reported quality of life, questioning the role of thyroid antibodies per se, on the quality of life.

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P1072

Iodine deficiency in pregnancy – is the situation in poland improving?

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Iodine deficiency is considered the most common preventable cause of brain damage worldwide. It is particularly important during pregnancy, as it influences not only mothers but their fetuses as well. The Polish model of iodine prophylaxis is based on obligatory household salt iodization and recommendation of iodine-containing supplements for pregnant women. The aim of the study was to assess the current iodine status of pregnant women and to compare it with earlier results.
Material and methods
1208 pregnant women aged 16-46 years (median 29 years) were included. 911 of them (75.4%) were investigated between 2007 and 2011, remaining 297 (24.6%) were studied in 2017. Signed informed consent was obtained from every participating woman. The urinary iodine concentration (UIC) in casual morning sample was assessed by Sandell-Kolthoff reaction. Thyroid volume was measured by ultrasound. Iodine supplements intake was assessed by a questionnaire. The study protocol was approved by the Local Ethics Board.
Results
The studied population of pregnant women proved to be iodine insufficient: median UIC was 94.9 mcg/l (lower quartile – 61.85 mcg/l, upper quartile – 149.0 mcg/l). The UIC significantly increased between 2007-2011 and 2018 (median 92.47 mcg/l and 111.45 mcg/l, respectively; $P=008$), but still did not meet iodine sufficiency criterion (between 150 and 249 mcg/l). In only 17.4% of investigated women, UIC value was within the optimal range of 150 to 249 mcg/l: 17.3% between 2007 and 2011, and 17.5% in 2018. 62.2% of pregnant women were taking iodine supplements: 63.3% of women investigated between 2007 and 2011, and 58.6% in 2011 ($P=0.14$). The median thyroid volume in the investigated group was 11.8 mL (lower quartile 9.2 mL, upper quartile 15.0 mL). There was no significant difference in thyroid volume between two groups: 11.9 mL between 2007 and 2011, and 11.6 mL in 2017.
Conclusions
Although during last 5 years iodine status of Polish pregnant women has improved, it has not reached a sufficiency level. Therefore the current Polish iodine prophylaxis model should be adjusted to provide pregnant women with adequate iodine intake.

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Serum thyroglobulin as a biomarker of iodine status in pregnant women

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Serum thyroglobulin (Tg) is a biomarker used to assess iodine nutrition status, but data in pregnant women are scarce.
Objectives
To determine serum Tg concentration in Spanish healthy pregnant women, and to evaluate its relation with yoduria (UIC), thyroid volume, iodine intake and thyroid function throughout pregnancy.
Methods
Longitudinal study in pregnant women with no history of thyroid disease, recruited in 2 obstetric centers of Pamplona (Spain) at the first antenatal visit. We performed anamnesis, iodine intake questionnaire, thyroid ultrasound, and UIC in a single visit. Thyrotropin (TSH), free thyroxine (fT4), antiperoxidase and antithyroglobulin (anti-Tg) antibodies were determined in the three trimesters, and Tg in the first and third trimesters. We compared Tg concentrations in women according to the consumption of iodized salt, milk intake and pharmacological iodine supplements.
Results
We evaluated 100 pregnant women in the 10th gestational week, 92% Caucasian. To establish thyroglobulin values we excluded multiple pregnancies ($n=2$), women with positive anti-Tg antibodies ($n=14$) and/or nodular goiter ($n=2$), leaving a population of 82 women. The median Tg was 14.1 µg/l. Only 1 woman had Tg$>$ 40 µg/l (Tg 42.3 µg/l in the third trimester). Tg at 9th gestational week ($n=65$) was lower compared with Tg at 37th gestational week ($n=20$): 12.4 vs 22.8 µg/l; $P<0.001$. Women with anti-Tg antibodies had lower Tg values than those with negative antibodies (Tg 6.44 vs 14.1 µg/l; $P=0.007$). Five of the 14 women (35.7%) with positive anti-Tg antibodies, had undetectable Tg concentrations (<0.2 µg/l). The median yoduria was 251 µg/l (188.5-368.5). No correlations between serum Tg concentrations and UIC, thyroid volume, TSH or T4l concentrations were found. Women who started iodine supplementation (200 µg/daily) at least 1 month before pregnancy, had lower median Tg, compared to those who started at the detection of pregnancy, and those with no iodine supplementation (Tg 10.8 µ/l vs 13.4 µ/l vs 23.4 µg/l respectively; $P=0.030$). We found no statistical differences in Tg concentrations according to the consumption of iodized salt (no consumption, since pregnancy detection or pre-pregnancy) or according to milk intake (<1, 1–3 or >3 daily servings).
Conclusions
In our population serum Tg does not correlate with yoduria, thyroid volume, thyroid function, use of iodized salt or milk intake. Starting iodine supplements at least 1 month before pregnancy is associated with lower Tg.

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Metabolic signature of hypothyroidism indicating higher cardiovascular risk

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Hypothyroidism is associated with higher risk of cardiovascular disease and increase of blood lipids. Previous evidence indicates that high dosage of levothyroxine could be cardiotoxic. There are fewer data describing mortality in subjects after treatment and stabilization of thyroid diseases and there are no data related to subjects with treated hypothyroidism. Aim of this study was to investigate correlations between the cardiovascular risk and metabolic status [Resting Energy Expenditure (REE),and Respiratory Quotient (RQ)], body composition and levothyroxine dosage in a population of patients affected by hypothyroidism. Twenty-five subjects (BMI$=28.4\pm5.5$ kg/m^2, range: 52.3–112.9 kg; age 52.6 ± 13.1 years) affected by hypothyroidism were analyzed. The cardiovascular risk was evaluated using skin autofluorescence via Age Reader instrumentation as well as estimated by Procam and Framingham index. Anthropometric and hormonal parameters (TSH, FT4 and FT3) were evaluated at baseline. REE was measured by indirect calorimetry and fat mass was evaluated by Air Displacement Plethysmography. Fourteen subjects had a high

cardiovascular risk (HCVD group) and 11 had a low cardiovascular risk (LCVD group). Comparing REE (measured vs predicted, %), fat mass (kilograms) and levothyroxine dosage (mcg) in HCVD and in LCVD group, a significant difference ($P < 0.05$) was found at baseline. The HCVD group showed lower REE %, higher fat mass and higher dosage of levothyroxine, compared to LCVD group. No significant differences were found in metabolic parameters (TSH, FT4, FT3) and in lipid profile (total cholesterol, HDL, LDL, triglycerides) between HCVD and LCVD. Patients with hypothyroidism treated with high dosage of levothyroxine had a major risk to develop a cardiovascular disease, a reduced REE and an excess of fat mass. Therefore, this study suggests that, among subjects affected by hypothyroidism, a reduced REE, an increased fat mass and a higher dosage of levothyroxine could be predictive of an increased cardiovascular risk.

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Abstract withdrawn.

P1076

Effectiveness of radioiodine treatment for toxic adenoma

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Objective
The purpose of this study was to assess clinical outcomes of patients with toxic adenoma (TA) treated with Radioactive Iodine (RAIT) in a tertiary hospital over a period of 8 years. We also analysed the influence of age, gender, TSH at diagnosis and anti-thyroid drugs (ATD) previous to RAIT on the cure rate.
Methods
Retrospective analysis of clinical records of all patients with TA submitted to RAIT between 2008 and 2015. The influence of demographic variables (age and gender) as well as clinical ones (TSH at diagnosis, iodine activity administered and previous ATD) on effectiveness of RAIT, 1 year after last treatment, was tested. Treatment success was defined by the achievement of euthyroidism or hypothyroidism 1 year after the last RAIT administration. For statistical analysis we considered a confidence interval of 95% ($sig < 0.05$).
Results
Over 8 years, 138 patients (female 110; male 28) mean age of 60.3 ± 14.6 years-old with TA were submitted to radioiodine treatment. Most patients were submitted to 10 or 5 mCi (61.8%–10 mCi; 35.8%–5 mCi) in a total of 145 treatments. Thirty-nine patients were lost for follow-up (28.3%). The global cure rate was of 82.8%. Hypothyroidism was observed in 32.3%. Age, gender and TSH at diagnosis had no influence on the outcome. Previous ATD was negatively correlated with the effectiveness of the radioiodine treatment. The cure rate achieved with activities of 5 and 10 mCi was slightly different, 75.6% and 88.7% respectively, but not statistically significant.
Conclusion
One year after RAIT, the cure rate of TA patients treated with an activity of 10 mCi was of 88.7% (euthyroidism 54.7% + hypothyroidism 34.0%); with an activity of 5 mCi was of 75.6% (euthyroidism 51.2% + hypothyroidism 24.4%). It is likely that for a longer period of follow-up these results might be different. Administration of ATD before radioiodine had a negative impact in therapy effectiveness.

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Effective complex treatment of endocrinous ophthalmopathy (EO) with ophthalmic hyperthyroidism resistent to steroid therapy

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Methods
With the purpose of evaluation of the condition of microlymphocirculation and the efficacy of lymph-stimulating medicines patients are divided into 2 groups: the reference group (p41) - traditional treatment (Thyrozol, Anaprilin). The main group (p16) – traditional treatment + Dalargin (Tyr-D-Ala-Gly-Phe-Leu-Arg, equivalent of leu-enkephalin) 1mg (per 2.0 0.9% NaCl) SC into the lateral part of the eyes No.7. Fluorescent lymphangiography, lymphoscopy, determination of the volume of lymphocirculation were performed before and after the treatment (3, 6, 12 months) for the purpose of comparative evaluation of the efficacy of the treatment.
Results
Already 3 months after the treatment with Dalargin, results in the main group reached the indicators of healthy people: reduction of the volume of lymphocirculation by 32% in the reference group and 72% in the main group; improved microlymphocirculation by 21.7% compared to the reference group; exophthalmometric values 3 months later approached the normal ones, and the effect was maintained during 12 months of observations.
Conclusion
1) dysfunction of the filtration and circulatory functions of the local and systemic lymphatic systems is observed in case of EO.
2) application of Dalargin in case of EO which is resistent to steroid therapy is effective, safe and pathogenetically substantiated.
3) lymphotropic subcutaneous periorbital application of the medicine increases the efficacy of traditional therapy.
4) the efficacy of the medicine in case of lymphotropic method of injections lasts 4-8 times longer and reduces the aggravation of the symptom by 6%.

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Diminished levels and defective suppression function of Tr1 cells is observed in patients with autoimmune thyroiditis

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Context
T regulatory type 1 (Tr1) cells are a subpopulation of T lymphocytes (CD4 + CD49 + LAG-3 + IL-10 +) lymphocytes that exerts a significant immunosuppressive effect. However, its possible role in autoimmune thyroid disease (AITD) had not been explored so far.
Objective
To analyze the levels and function of Tr1 cells in peripheral blood and thyroid tissue of patients with AITD.
Design
Cases and controls, observational study.
Setting
Department of Endocrinology, Hospital Universitario de la Princesa, Madrid, Spain.
Patients
Thirty-eight patients with AITD (23 with Grave's disease and 15 with Hashimoto thyroiditis) and twenty-six controls.
Intervention
Multi-parametric flow cytometry and immunofluorescence techniques were used to analyze the levels in peripheral blood ($n = 38$) and thyroid mononuclear cells ($n = 5$). An *in vitro* assay of suppression of cellular activation and cytokine release was performed to study the function of Tr1 cells. Main Outcome Measure: Levels and function of Tr1 cells in AITD patients and controls.
Results
Levels of Tr1 cells were significantly diminished in peripheral blood from AITD patients. Functional studies showed that Tr1 cells from AITD patients exhibit a diminished suppressive function compared to healthy controls. Tr1 levels were associated with disease severity, and auto-antibody titers.

Conclusions
The low levels of Tr1 cells and its diminished function may have a relevant role in the defective immune-regulatory function characteristic of AITD patients.

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Thyroid amyloidosis mimicking medullary thyroid carcinoma

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Introduction
Amyloid accumulation in the thyroid gland leading to a clinically detectable mass is a rare clinical entity. The diagnosis of thyroid amyloidosis can be confused clinically as well as cytologically with both colloidal goiter or neoplastic processes of the thyroid. We report a case of thyroid amyloidosis that was initially misinterpreted as medullary thyroid carcinoma (MTC) clinical and cytological examination.
Case
A 24 years old man with chronic renal failure admitted to our hospita with rapidly progressive enlargement of a neck mass. He was suffering from renal failure for at least 10 years secondary to nephrolithiasis and was on 3 day/week hemodialysis after the rejection of renal transplantation 2 years before. He had dysphagia and dyspnea for about 5 months. Further workup demonstrated multinodular goiter with compressive symptoms and substernal extension. He had multiple nodules with the largest diameter of 80 mm in ultrasonography. Serum TSH was1.68mIU/L (0.27–4.2), free T4 was1.01ng/dL (0.9–1.7), free T3 was2.84ng/dL (1.8–4.6) and thyroglobulin was 758 ng/mL (0–78). Anti-thyroglobulin and anti-thyroid peroxidase antibodies were negative. His calcitonin level was high which was suggestive for possible diagnosis of MTC (12.6 pg/mL normal:2-8 pg/mL). Fine needle aspiration cytology of the largest nodule displayed MTC. 24 hour urine catecholamine levels were within the normal range and computerized tomography of adrenal glands revealed no pathology. Total thyroidectomy was performed and the final histopathological diagnosis was thyroid amiloidosis.
Conclusion
Although amyloid deposition in thyroid is a well known fact in MTC, it should be remembered that it is not a histological finding exclusive of this disease. In patients with a rapidly enlarging thyroid gland presenting with dysphagia, dyspnea, or hoarseness, amyloid goiter should be included in the differential diagnosis particularly when the patient has a chronic disease that might be associated with amyloidosis.

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P1080

EMPATHY: a new tool for identifying the most suitable thyroxin formulation in hypothyroid patients

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Hypothyroidism therapy is based on the administration of appropriate dose of L-thyroxine (L-T4). Absorption of L-T4 takes place in the duodenum and upper tract of the small intestine (jejunum), is maximal when stomach is empty, and is affected by a number of gastrointestinal disorders, including Helicobacter pylori–related gastritis, as well as ingestion of drugs, dietary fibers, and herbal remedies. Failure to achieve a good control of disease may be due to malabsorption in 40% of cases, or to poor compliance to L-T4 therapy in 60% of cases. During the past few years, various L-T4 formulations (in tablets, soft-gel capsules and liquid solution) have become available for clinical use. Liquid or gel formulations may be considered in subjects with hampered L-T4 absorption or who are not adherent to breakfast waiting time after L-T4 administration. Questionnaires to assess adherence to therapies are available and also adapted to patients with hypothyroidism. On the contrary, there are no tools available to detect malabsorption disorders and then addressing the endocrinologist in choosing the most appropriate therapy. Here we present EMPATHY (Evaluation of Malabsorption in PATients with HYpothyroidism): a questionnaire consisting of 13 questions which may help the endocrinologist to identify malabsorption disorders and then choose the most appropriate L-T4 formulation for each patient. EMPATHY allows to evaluate not only lactose and gluten intolerances but also some other allergies (nickel, histamine, citric acid, cornstarch) and alcohol intolerance. We administered EMPATHY to 150 newly diagnosed hypothyroid patients (50 males and 100 females). Exclusion criteria were previous thyroidectomy for thyroid cancer, central hypothyroidism, diabetes, obesity, current L-T4 therapy and pregnancy. We recorded more than 3 dose adjustments in six months in 21 out of 150 (14%) patients completing questionnaire and in 42 out of 150 (28%) not completing questionnaire ($P=0.01$). After two months of replacement therapy, most of patients in the group completing questionnaire (110 out of 150, 73%) and 82 out of 150 (54%) in the other group achieve a good control of disease ($P=0.001$). EMPATHY resulted extremely useful in the clinical practice allowing a better personalization of L-T4 replacement therapy and then a more rapid achievement of good control of the disease with smaller need of subsequent dose adjustments.

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Coincidental prolactinoma and parathyroid adenoma in a patient with negative MEN1 and MEN4

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Introduction
Multiple endocrine neoplasia type 1 (MEN 1) is associated with neoplasia and hyperfunction of the parathyroid and pituitary glands, pancreatic islet cells, and neuroendocrine cells of the gut. Many authors advocate routine subtotal or total parathyroidectomy and autotransplantation for these patients. Here we demostrate negative MEN1 and MEN4 gene mutation analysis in a case with prolactinoma and a large parathyroid adenoma that could not be localized with preoperative imaging techniques.
Case
A 21-year-old man applied with a 8 years history of recurrent renal stones and increased serum calcium (11.25 mg/dl [Normal–9-10.5mg/dL]), alkaline phosphatase (147 U/L [Normal-30-120U/L]), serum parathyroid hormone (137 pg/l[Normal–10-60pg/mL]) and low phosphorus (2.1 mg/dl[Normal 3–4.5mg/dL]). Localization studies by imaging techniques (neck ultrasonography, Computed tomography and Tc-99m MIBI scintigraphy) failed to determine the number and location of diseased parathyroid glands. In addition, laboratory studies demonstrated elevated serum prolctine (246, Normal - 4.79-25.3 ng/mL). Other pituitary hormones were normal. Pituitary magnetic resonance imaging revealed 7.5 mm pituitary adenoma. He was started on cabergoline. Germ-line mutation analysis for *MEN1 and* Multiple endocrine neoplasia type 4 (MEN4) genes were negative and he had no familial history of endocrine tumors. Intraoperative parathyroid exploration demostrated a 3 cm paratyhroid adenoma. Histopathpolohical diagnosis was compatiel with parathyroid adenoma. There was no hypocalcemia or recurrence with a follow-up of 14 months.
Conclusion
Coexistence of hyperparathyroidism and prolactinoma in a young patient might not be always related to MEN1. A careful intraoperative exploration by an experienced parathyroid surgeon can be the best approach when hyperparathyroidism is diagnosed biochemically despite negative localization.

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How should thyroid-related quality of life be assessed? Standard recall measures compared with here-and-now measures

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Introduction
Some methodologists have raised concern about the validity of the standard method of assessing patient-reported outcomes, i.e. retrospective questionnaires. Repeated momentary measurements have been introduced to avoid recall bias and provide ecological validity. Although having theoretical advantages, the measurement properties remain unsubstantiated. This study examines the relationship between the retrospective thyroid-related quality of life patient-reported outcome measure ThyPRO and a momentary version of ThyPRO.
Methods
Eighty-three hyperthyroid patients were included to answer questions about their thyroid-related quality of life. Twelve momentary items from four multi-item scales were administered thrice daily via a smartphone application during 28 days. On day 28, the original retrospective ThyPRO was administered, thus the same period was covered by two different measurement methods, enabling head-to-head comparison. Correlations, differences, and levels of agreement were examined across all four scales. Further, it was explored if the two most substantiated forms of recall bias were evident (the peak effect and the end effect).
Results
Retrospective and averaged momentary ThyPRO ratings were highly correlated with Pearson correlations of 0.74–0.88. However, retrospective ratings provided significantly higher results, i.e. worse quality of life, on all scales with varying magnitude. Bland-Altman plots showed a skewed distribution, indicating low levels of agreement. Results supported the presence of the peak effect when measuring tiredness, but not on the remaining scales. There was partial support for the presence of an end effect, which was found in two of four scales.
Conclusion
Retrospective ThyPRO ratings and the average of momentary ThyPRO ratings were highly correlated, but provided significantly different results on the four tested scales, with higher scores in the retrospective rating. Only limited evidence was found to support the peak effect and the end effect. Thus, other possible explanations for the observed differences should be examined. The differences in scores were of clinically relevant magnitudes, why the two measures should not be interchanged. In most clinical studies the retrospective rating will be useable, however when designing clinical studies the measurement method should be carefully selected depending on the aim of measurement. To identify the most valid measurement method prospective analysis will compare responsiveness to change.

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P1083

Radiofrequency ablation of the autonomously functioning benign thyroid nodules: 5-years follow-up

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Introduction
The aim of this study was to evaluate the safety, efficacy and side effects of radiofrequency (RF) ablation for treating autonomously functioning thyroid nodules (AFTN). The study included the data of single centre.
Material and methods
The analysis included the results of the treatment of 127 patients with autonomously functioning benign nodules, received in the Samara Oncology Center in 2012–2015 years. All patients had high level of thyroid hormones and low level of thyreotropin. In all of them scintigraphy determined hot nodules. All the patients underwent fine needle biopsy twice. During the follow-up nodule volume and thyroid function were evaluated.
Results
The mean follow-up was 47.2 ± 13.5 months. 61 (48.0%) patients underwent 1 session of RFA, 54 (42.5%) patients – 2 sessions due to the big initial nodule size (more than 3 cm). In 12 (9.4%) patients after ablation and normalization of hormones levels during 3–6 months the minor nodule became active. That patients underwent ablation of this nodule too. Levels of triiodothyronine, free thyroxine, and thyrotropin reached normal in 2–3 weeks after RFA. During 5-years of follow-up hormone status remained normal. No serious complications such as thyroiditis, voice change, and hematomas were observed. RFA was an effective method for treating hot nodules.
Conclusion
RFA was effective, safe and repeatable procedure for treating autonomously functioning benign thyroid nodules.

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Clinical and genetic study of autoimmun thyroid disease in a Tunisian multigenerational family

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Autoimmune thyroid diseases (AITD), which include Hashimoto thyroiditis (HT), Graves' disease (GD) and primary idiopathicmyxoedema (PIM), are recognized by their clinical and genetic heterogeneity. In this study, we have carried on a global approach gathering 20 year genetic and clinical data on a Tunisian multigenerational family (Akr). Our purpose was search for a combined genotype involved in AITD susceptibility using 33 gene polymorphisms. The Akr pedigree is composed of more than 400 members distributed on 10 generations. Clinical follow-upwas performed by appreciation of the thyroid gland and measurement of both thyroid hormone and auto antibody levels. We used FBAT software to test for association between gene polymorphisms and AITDs. Clinical follow-up has showed that the number of AITD patients has increased from25 to 78 subjects subdivided on 51 cases of GD, 22 PIM and 5 HT. Concerning genetic analysis, our study has revealed new gene association when compared with our previous analysis (considering single genes). Thus, PTPN22, TG and VDR gene polymorphisms have became associated with p-values ranging from4.6 10^{-2} to 4 10^{-3} when consideredwith other genes on the same chromosome; giving evidence for gene interaction. The most significant association was found with the MHC region (p7.15 10^{-4}). Moreover, and among gene polymorphisms explored, our analysis has identified some of them as AITD biomarkers. Indeed, PDS gene polymorphisms were associated with either exophthalmia or goiter (p-values from 10^{-2} to 10^{-3}). In conclusion, our study gives evidence for gene interaction in AITD development confirming genetic complexity of these diseases.

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High endocan level is associated with Graves' disease

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Endocan has been suggested as a marker for endothelial dysfunction. Some evidence exists that Graves' disease may be associated with impaired endothelial function. The aim of the study was to evaluate serum endocan, endothelial growth factor (VEGF) and carotid intima media thickness (CIMT) in patients with Graves' disease. Thirty one newly diagnosed patients with Graves' disease and 31 healthy volunteers with similar age and sex were examined. Serum endocan, VEGF levels and CIMT were measured in the patient group both before antithyroid treatment and after euthyroidism achieved and compared with the control group. Serum endocan levels were higher in the hyperthyroid Graves' group than the control group (0.68 (0.18-1.21) vs 0.49 (0.11-1.88) pg/ml, $P = 0.002$). There was no significant difference in Graves' group after euthyroidism was achieved and the control group (0.57 (0.14-0.96 vs 0.49 (0.11-1.88) pg/ml, $P > 0.05$). Serum VEGF levels were not significantly different in the Graves' and control group ($P > 0.05$). CIMT was higher in the hyperthyroid Graves' group than the control group (0.68 ± 0.07 vs 0.47 ± 0.06 mm, $P < 0.001$). Decrease in CIMT was observed after euthyroidism achieved, however, it was still higher than the control group (0.59 ± 0.05 vs 0.47 ± 0.06 mm, $P < 0.001$). Serum endocan levels were correlated negatively with TSH ($P < 0.01$); positively with fT3 ($P = 0.01$), fT4 ($P < 0.01$), Anti-Tg ($P < 0.05$) and Anti-TPO

($P<0.001$). In multiple linear regression analysis fT3 level was the most important predictor for endocan levels ($F=5.664$, $R^2=0.106$, $P<0.05$). In conclusion, our findings suggest that serum endocan levels are increased and associated with fT3 in patients with Graves' disease.

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P1086

Segregation of S292F TPO gene mutation in three large Tunisian families with thyroid dyshormonogenesis: evidenceof a founder effect

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We aimed to identify causal mutation(s) in 13 patients with thyroid dyshormonogenesis (TD) from three consanguineous Tunisian families. A 12-year clinical follow-up showed phenotypic variability ranging from the presence to the absence of goiter, sensorineural deafness, and mental retardation. Genetic analysis using microsatellite markers within two candidate genes (TPO and PDS) gave evidence of linkage with the TPO gene. Sequencing of its 17 exons and their flanking intron-exon junctions revealed the previously described c.875C>T (p.S292F) mutation in homozygous state. No additional mutations were found in either a 900 bp of the TPO gene promoter or PDS gene. In silico analysis showed that p.S292F mutation might reduce the catalytic cavity of the TPO which would restrict access of a potential substrate to the catalytic pocket. Using 4SNPs and one microsatellite marker in the TPO gene, an associated haplotype: G-C-G-G-214 was found, giving evidence of a founder mutation.

Conclusion

This is the first description of a TD causing mutation in Tunisia and thus may help to develop a genetic screening protocol for congenital hypothyroidism in the studied region. Although structural modeling suggested a pathogenic effect of this mutation, functional studies are needed. Additional causing and/or modifier genes, together with late diagnosis could explain the clinical variability observed in our patients.

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P1087

When thyroid pathology becomes an emergency: about four cases

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Introduction

The thyroid emergency is a rare and life-threatening condition. These are severe complications of benign thyroid disease.

Patients and method

We report cases of thyroid pathology constituting an emergency and have been collected over 2 years in the department of endocrinology of the CHU Mohammed VI of Marrakech.

Results

Four cases of thyroid emergency were reported: three cases of acute thyrotoxic crisis (CAT) and one case of thyroid abscess. All patients were young, aged 20, 32, 40 and 45 years and were all female. The first case of CAT had complicated a disease of basedow, the other two were on multi-hetero-nodular toxic goiter. All three were revealed by an acute polymorphic table evoking the CAT. The case of thyroid abscess was revealed in a postpartum patient by a sudden increase in the volume of a pre-existing goitre with inflammatory signs. Evolution was good in all patients.

Discussion

Thyroid emergency is a serious pathology involving CAT and myxoedematous coma in addition to infectious pathology. The latter remains exceptional. A rare occurrence in developed countries, it is still present in disadvantaged areas and remains subject to significant mortality if there is no diagnosis and early and adequate management.

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P1088

Dysthyroidism and chromosomal aberrations

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Introduction

Dysthyroidism is not uncommon during chromosomal aberrations. The objective of this work is to study the characteristics of this association at the epidemiological and clinical levels.

Methods

This is a retrospective study of 27 cases of patients with trisomy 21 chromosomal abnormalities (6 cases), klinefelter syndrome (4 cases) and Turner syndrome (17 cases) genetically confirmed, collected at endocrinology service at Sfax University Hospital (CHU) over a period of 20 years (1997–2017) during which we selected patients with thyroid disease.

Results

Six out of 27 patients had a dysthyroidism with a prevalence of 22.2%. Hypothyroidism was found in 5 patients. The average age was 19.6 years old. The mean FT4 was 5.75 pmol/l and the average TSH was 113.1 µmol/l. Only one case of hyperthyroidism was collected in a 9-year-old trisomy 9 with a FT4 of 24.3 pmol/l and a TSH of 0.015 µmol/l. Antithyroid antibodies was positive.

Conclusion

The prevalence of dysthyroidism during chromosomal aberrations is estimated at 25% to 60% in the literature, dominated by hypothyroidism and autoimmune origin in most cases. Thus systematic evaluation for thyroid dysfunction should be made in this population to detect such anomalies.

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Riedel's Thyroiditis with Hypothyroidism and Hypoparathyroidism

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Riedel thyroiditis (RT) is a rarest form of thyroiditis, and characterized by dense fibrosis of the throid gland and infiltration into surrounding tissues. RT generally presents with local symptoms association with compression and also fibrotic process can impact thyroid and parathyroid functions. We report a case with RT which presents with compression findings and also hypoparathyroidism and hypothyroidism. 30 year old women visited our outpatient clinic with a complaint of neck mass and hoarseness. The symptoms had begun 20 days ago and had been followed by dyspnea. This patient had previously diagnosed with hypothyroidism and after hypoparathyroidizm approximately 6 mounths before and she had underwent treatment. She had been taking L- thyroxine, vitamin D3 and calcium preparat. Thyroid examination revealed a diffuse thyroid enlargement with very firm tissue. She had also stridor in rest. Thyroid function tests revealed thyroid stimulation hormone of 13.22 mIU/l (normal range, 0.4–3.7), showed hypothyroidism. Levels of thyroid antibodies were negative. Blood calcium was 7.8 mg/dl (normal range:8.8–10.6 mg/dl). Her parathyroid hormone level was12.7 ng/l(-normal range:15–65). Other biochemical tests were normal. Thyroid ultrasound demonstrated asymetrically enlarged thyroid gland with decreased vascularity, and showed a 4 cm mass in the left lobe and 3 cm mass in the right lobe. There was right shift of the trachea. There were no enlarged pathologic lymph nodes in the neck. Computerized tomography (CT) scan suggested that multinoduler guatr with a largest mass in the left lobe of the thyroid which push the trachea and caused tracheal stenosis. USG-guided tru-cut biopsy was performed on the nodule of greatest size. Histopathology exam showed that the thyroid gland was destroyed and extensively replaced by dense kollogen fibrous tissue with mononuclear cells infiltration. There was no evidence of malignancy and resultly riedel thyroiditis was confirmed as a diagnose. Prednisolon 40 mg/day was started and has been tapered during six months. After six month of treatment the symptoms improved and neck mass size decreased, and in ultrasound examination trachea was normal. After 6 months of follow up, now the patient is euthyroid with levothyroxine replacement (her needs reduced with time), and pth level was increased. In conclusion the appearance of hypoparathyroidism in Riedel's thyroiditis is a rare situation. Clinicians should be aware of RT, which presents as

stony hard thyroid with hypothyroidism and unexpected hypoparathyroidism. The response to treatment was good with prednisolon.

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Our experience in the first year of radiofrequency ablation of benign thyroid nodules

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Purpose
At the beginning of 2016, radiofrequency ablation of benign thyroid nodules began to be carried out at the Central University Hospital of Asturias (Spain). The aim of this study was to evaluate the results obtained by the moment with the aforementioned technique.
Methods
It is a descriptive study carried out through the data obtained during the process and the subsequent analytical and ultrasonographic follow-up. In addition, patient surveys have been conducted, mostly by telephone.
Results
• *General data.* 24 patients undergoing treatment (18 women and 6 men), with a mean age of 52.7 (minimum 36 and maximum 83).
• *Evolution of size. Revision to the first month (n=20):* average reduction of 35.765% (median: 36.5, maximum: 69, minimum: 7). *Revisions at 3-6 months (n=10):* average reduction of 59.7% (median: 65, maximum: 88, minimum: 33). *Review at 8-9 months (n=10):* average reduction of 50.7% (median: 54, maximum: 84, minimum: 15). *Review at 11-14 months (n=2)*: average reduction of 89%.
• *Thyroid function.* 94.7% of euthyroid patients prior to radiofrequency remained euthyroid.
• *Pain during the intervention*. 89.47% of patients said they did not feel pain. 5.25% moderate pain and 5.25% intense pain.
• *Complications.* Local discomfort 63%, (83.33% mild, 16.67% moderate). Hematoma in 26.31% (80% mild, 20% moderate). Mild dysphagia 5.26%. There was no dyspnea or serious complications in any patient.
• *Subjective improvement.* 100% presented subjective improvement. In sensation of cervical bulk 84.21%, aesthetically 73.68%, dysphagia 63.15%, dyspnea 36.86%.
• *Satisfaction.* 78.94% were very satisfied with the treatment, 10.52% satisfied, 10.52% intermediate satisfaction. None was dissatisfied.
• *Repetition.* 100% of patients would repeat the radiofrequency treatment if necessary
Conclusion
• There have been marked reductions in the size of the nodules. This decrease is echographically appreciable from the first month, showing in most cases an increase in the reduction in subsequent revisions.
• Thyroid function is not affected by the use of radiofrequency therapy.
• The technique, in most cases, is not painful.
• No serious complications have occurred. It is seen as the main complication local discomfort, being mild in the vast majority of occasions.

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P1091

Utility of 99 Tc-MIBI scintigraphy for the assessment of thyroid nodules with bethesda III cytologies

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Introduction
Up to 30% of the thyroid nodules studied with fine needle aspiration biopsy (FNAB) are reported as Bethesda III, a category that does not rule out malignancy. One technique that could help to decide if there is a surgical indication is (99 m) Tc-sestaMIBI scintigraphy (MIBI).
Material and methods
All patients with a Bethesda III result were prospectively included, and 99 Tc-MIBI scintigraphy was performed prior to surgery. All exams, including ultrasonography, FNAB, cytological diagnosis and scintigraphic exams were perfomed in our hospital. (99 m) Tc-sestaMIBI scintigraphy reports were based on contrast retention at 10 minutes and 3 hours after the radiolabeled compound injection, with gradation of intensity in both moments, considering pathological uptake a moderate-intense retention in any of them. These results were eventually compared with the histological results after surgical intervention.
Results
Eighty-four patients with a 99Tc-MIBI scintigraphy underwent surgery, 68 (80.9%) women, mean age 52.4 ± 13.8 years. 99Tc-MIBI scintigraphies results were reported as benign in 39 (46.4%) and pathological in 45 (53.6%). After surgery 19 (22.6%) cases were reported as thyroid cancer (TC) (12 papillary, 5 follicular and 2 poorly differentiated) and 65 (77.4%) as benign. 38 (58.5%) patients with histological result of benignity did not show pathological uptake in MIBI and 27 (25.6%) did (59,2% at 10 minutes and the rest at both phases). Only one patient with TC (5.3%) did not show a pathological uptake in MIBI. With these results the pathological uptake in MIBI shows a sensitivity of 94.7% and a specificity of 58.5%, with a positive predictive value of 40% and negative predictive value of 97.44%($p < 0.001$ in chi square test).
Conclusion
We confirm that 99 Tc-MIBI scintigraphy is a useful technique for the identification of benign nodules after the Bethesda III result in cytology with a high negative predictive value. We think that patients with a Bethesda III cytological in a thyroid nodule FNAB and a non pathological MIBI uptake could be undergo clinical follow up without performing surgery.

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Shopping trip and a thyroid storm

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A previously fit and well 27 year old Ghanaian male was brought to hospital by his cousin due to new behavioural changes. The patient was described by his cousin as a normally reserved, self-sufficient man who had become a polar opposite 'irritable' personality that 'spent extravagantly'. He repeatedly claimed to be 'God's protection' and responded aggressively to visual hallucinations. This had resulted in social exclusion and loss of employment. There was no significant family history or history of substance or alcohol misuse. Physical assessment was limited due to poor patient co-operation. Bedside observations revealed a marked resting tachycardia (121 bpm). Oxygen saturations, blood pressure and temperature were all normal. There was no apparent focal neurological deficit or neck rigidity. The remaining physical examination was positive only for a non-tender goitre and hand tremors. Electrocardiography confirmed sinus tachycardia. Computerised tomography (CT) head scan was normal and lumbar puncture was unsuccessful despite sedation. Initial investigations revealed a mild inflammatory response without electrolyte disturbances. He was treated empirically for meningoencephalitis, however, further urgent investigations confirmed marked hyperthyroidism with free T4 95 pmol/l (10–19.9 pmol/l) and TSH < 0.01 mU/l (0.35–5.5 mU/l). A diagnosis of thyrotoxic psychosis was made. He was commenced on high-dose carbimazole and propranolol 160mg daily in divided doses with little effect. Hydrocortisone, lithium and cholestyramine were subsequently added to help achieve euthyroidism with a consequential improvement in his mental state. A total thyroidectomy was performed to achieve definitive control. He was successfully discharged a few days later on levothyroxine and was given a supporting medical letter to help to cancel the multiple phone contracts and loans that he had accumulated during his thyrotoxic state. Histological evaluation of the excised thyroid gland confirmed Graves' thyrotoxicosis.
Conclusion
Thyrotoxic psychosis, although rare, should be considered in all patients with behavioural disturbances to allow early treatment, prompt control and improved outcomes.

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P1093

Should tocilizumab be a second-line treatment of active, moderate-to-severe Graves' Orbitopathy?

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Introduction
Graves' orbitopathy (GO) is the most common extrathyroidal manifestation of Graves' disease. The first-line treatment are intravenous corticoids in active moderate-severe GO. Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor which has been approved for the treatment of rheumatoid arthritis and is in its research stage for patients with corticosteroid-refractory GO.
Objectives
To assess the experience with tocilizumab in patients with GO at the University Clinical Hospital of Salamanca.
Material and methods
Retrospective analysis of four patients treated with tocilizumab for GO since 2014. The CAS was ≥ 3 and TSI antibodies were positive. An intravenous dose of 8 mg/kg was administered every month. The end of the treatment was dependent on clinical improvement (CAS ≤ 2) or negative results for TSI antibodies.
Results
The average age was 45 ± 9.5 years, and 50% of the patients were male. Half of the patients were active smokers and the rest were ex-smokers. Two of them were diabetic. They all presented bilateral moderate-severe GO and three of them had previously received corticoids (4.5 g doses) without any improvement. One patient had received treatment with rituximab, with no results. The average time from the last dose of corticosteroids and the administration of tocilizumab was 5 months. After 6.5 ± 2.6 cycles all the patients showed an improvement of the CAS (6 ± 2.3 before the treatment and 2.3 ± 0.5 after the last cycle ($P = 0.036$)). All the patients showed an improvement of exophthalmos, visual acuity and ocular motility. Two patients required decompression surgery and one patient required radiotherapy. TSI antibodies returned to normal values in all cases. The follow-up since the last dose was 18.3 ± 6.3 months, without any recurrence. None of the described secondary effects were observed, although two of the patients showed asymptomatic CK elevation.
Conclusions
Tocilizumab may be an alternative to corticoids in patients with GO who do not respond to them or who have a contraindication. More studies are necessary to assess the effectiveness and safety of this drug.

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P1094

Features and determinants of hypothyroidism in patients with major beta thalassemia from Algeria.

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Introduction
Hypothyroidism is the most common endocrine pathology during Major Beta Thalassemia (MBT). The geographic area is considered a factor in establishing the prevalence and form of hypothyroidism in MBT. We have tried through this study to establish features and determinants of hypothyroidism in Algeria.
Patients and methods
Twenty patients middle-aged 27 years (20–46 years) (10 males/10 Females) hospitalized in Pierre Marie Curie Center, Hematology unit, Algiers. All patients have been tested for thyroid hormones levels: TSH/FT4/FT3. Results have been correlated with ferritin and hemoglobin levels, the type of chelation (Deferoxamine/Deferasirox) as well as the viral serology.
Results
The prevalence of hypothyroidism is 25%. In 15% it is a subclinical hypothyroidism (1M/2F) who have benefited from antibody dosing (Ab TPO, Ab TG), while 10% have a central hypothyroidism, it is about two sisters without statural or weight delay having a gonadotropic deficit among them one died by hypersplenism having refused the splenectomy. No correlation was noted between ferritin and TSH (P: -0.06) nor FT4 (P: -0.05). Neither the Beta thalassemia duration nor the degree of anemia nor the type of chelator nor hyperferitemia appears to be risk factors for hypothyroidism with respectively Odds ratio (0.16/0.23/0.73/0.73). Subjects with viral hepatitis are more exposed, but not significantly, to hypothyroidism regardless of its form compared to unaffected individuals (odds ratio: 1.67).
Conclusion
In this sample of the North African MBT form, hypothyroidism seems to be heterogeneous between borderline primary hypothyroidism and the central form rarely described in the published series of the South European MBT, which demonstrates the main role of the geographical factor. Furthermore, an association of central and peripheral form of hypothyroidism in the same patient is not to eliminate. The treatment of subclinical hypothyroidism is often necessary especially in patients inadequately controlled under chelation treatment which are at high cardiovascular risk by iron overload.

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P1095

Serum chemerin and other dyslipidemia markers in patients with autoimmune thyroiditis

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Aim
Chemerin, a recently discovered adipokine produced by the adipose tissue and liver, along with other atherosclerosis markers, was associated lately with metabolic syndrome and acts as chemoattractant for immune cells may also regulate immune cell properties. Autoimmune Hashimoto's thyroiditis even with sTSH levels corrected to be within the normal range values may be accompanied by dyslipidemia presenting increased total-C, TG, LDL-C, and Lp(a), all of which are potential risk factors for developing atherosclerosis. Previously we found significant correlations between serum chemerin levels and lipid and lipoprotein subfractions in nondiabetic obese patients. However, chemerin level and its association with serum lipid levels in Hashimoto's thyroiditis has not been fully investigated.
Methods
In the present study we measured the serum chemerin and other atherosclerosis marker levels by ELISA in 52 patients with Hashimoto's thyroiditis and in 34 age, gender and BMI matched controls.
Results
We did not find significant difference in serum chemerin levels between the patient and control groups (88.7 ± 16.8 vs 91.5 ± 15.9 ng/ml). However, significantly higher sTSH, LDL-C, Lp(a), apoA1 and apoB levels were found in patients compared to the controls. We found significantly positive correlations between serum chemerin levels and TG, non-HDL, leptin and CRP, age and BMI. In this study chemerin level negatively correlated with the HDL-C level. There was no correlation between chemerin and sTSH, fT3 and fT4, and anti-TPO levels. These findings were consistent even when comparing the subgroups of patients having their sTSH levels above and under 4 mU/l, nor when considering these groups and the controls. Leptin was found to be an independent predictor of chemerin in both patient and control groups.
Conclusions
Although serum chemerin is not elevated in patients with Hashimoto's thyroiditis, regardless their actual sTSH levels, patients with higher chemerin levels present impaired dyslipidemia markers associated with increased risk for atherogenesis. Therefore, chemerin may be a useful marker in atherosclerotic risk assessment in patients having Hashimoto's thyroiditis.

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P1096

Current iodine status in a Romanian school-aged children

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Introduction
Iodine deficiency is one of the most important cause of mental and physical disorders and is considered a public health issue. Previous studies reported the existence of iodine deficiency in several regions in Romania and its related

negative side effects on children's health. Therefore, Romania has implemented the universal salt iodisation (USI) since 2002.
Aim
The present study aimed to assess the current iodine status in Romanian school-aged children.
Subjects and methods
The study analysed data from a nationally representative sample – 624 children, aged 6–7 years old, covering 15 Romanian counties. Urinary iodine was measured using spectophotometric method, with ceramic ammonium sulphate. The iodine status of the target population was apreciated comparing the median urinary iodine value of the urine samples with WHO standards. The study was approved by the Local Ethics Committee. An informed consent from the parents was obtained.
Results
The median iodine value of 255.3 μg/l reflects a more than adequate iodine status of the surveyed population. The mean value of urinary iodine (275.6 μg/l) and its standard deviation (133.22 μg/l) showed a large dispersion of the results. Data were analysed and disscused in the context of previous studies. We report here a significant improvement in the iodine status of the children in Romania, reflecting an appropriate iodised salt household consumption.
Conclusions
In Romania, there is currently no iodine deficiency among school children in the context of the universal salt iodisation. In order to ensure an adequate prophylaxis of mild iodine deficiency, continuous iodine monitoring is required among schools in all urban and rural areas, and to correlate the iodine values with the other markers of iodine deficiency (neonatal TSH, thyroid volume).

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Primary thyroidal paraganglioma in a 60 years old female with thyroid goiter

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Primary Paraganglioma of Thyroid Gland is an extremely rare neuroendocrine tumor. Less than 50 cases have been reported up to date and its rarity is the reason why it's often mistaken for thyroid nodule or other thyroid neoplasms. In this case we describe the misleading results of ultrasonography followed by FNA-biopsy, which led to a total delay of two years until final diagnosis. A 60 year old female presented with a 38 mm right-sided thyroid module. An ultrasound guided FNA-biopsy was performed and the cytology report was suggestive of a follicular adenoma. A total thyroidectomy was suggested because of the large size and hyper vascularity of the nodule, which was performed two years after initial examination. The results of histological examination revealed a neoplasm morphologically following a nesting pattern (zellballen) with rich capillary network. Immunohistochemical staining of the neoplasm was positive for chromogranin, synaptophysin and CD56. Sustentacular cells were positive for S-100 and Ki-67 was lower than 1%. Staining was negative for thyroglobulin and calcitonin. Neck-adrenal MRI as well as chest CT were normal. She underwent blood tests for gastrin, chromogranin A, calcitonin, tumor markers and 24 h catecholamine urine test (CATU) along with 5HIAA and VMA, all of which were also normal except from chromogranin A: 487 ng/ml (normal values: <120 ng/ml). We have no evidence of recurrence up to date and we suggested to the patient to undergo molecular analysis for germline mutations of the genes encoding succinate dehydrogenase subunits, SDHD, SDHAF2, SDHC, SDHB and SDHA. Diagnosis of TP is always confirmed postoperatively and differential diagnosis also includes medullary thyroid carcinoma and hyalinizing trabecular adenoma. These three conditions need completely different surgical approach and a close post-operative follow-up testing. Despite its rare frequency thyroid paraganglioma should always be included in the differential diagnosis of hypervascular thyroidal lesions especially those with indeterminate or undefined cytological results.

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P1098

Management particularities of substernal goiter

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Introduction
The definition of a substernal goiter is not univocal, several definitions have been advanced. It poses difficulties by its therapeutic features and management. The aim of this presentation was to detail the particularities of the management of substernal goiters and their therapeutic difficulties.
Methods
This is a retrospective study carried out on 40 patients with substernal goiter admitted to our department and treated during a period of 5 years (from 2012 to 2017).
Results
They were 13 men and 27 women. The average age was 52 years. The main complaint was a cervical mass found in all cases, associated with signs of compression in 15 cases. The size of the mass ranged from 3 to10 cm with an average of 7 cm. The patients were in clinical euthyroidism in 33 cases. The radiological assessment included cervical examination ultrasound and cervico-mediastinal CTscan in all cases. A total thyroidectomy was performed in 26 cases and a loboisthmectomy in 14 cases. The cervical approach was sufficient in the majority of cases. We used sternotomy in two cases. The malignancy rate was 12%. It was a papillary carcinoma in four cases and medullary in one case. A central compartment dissection was practiced in five cases and lateral in 1 case. I^{131} remnant ablation was performed for papillary carcinomas with a dose of 50 to 300 mci. External radiotherapy was performed for the case of medullary carcinoma for curative purposes. All patients with benign goiters had a good outcome over the course of follow-up time.
Conclusion
Generally benign, the surgery of substernal goiter is more difficult than that of cervical goiter. The cervical approach is often sufficient; however, a sternotomy is sometimes needed. The prognosis depends on a good preoperative preparation and rigorous postoperative follow-up.

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P1099

A case of respiratory arrest associated with sepsis induced myxoedema coma

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A 58-year old previously independent man with background of poorly-controlled hypothyroidism, T2DM, hypertension, ischaemic cardiomyopathy, and CKD presented to hospital feeling generally unwell, with a dry cough. His regular medications included anti-hypertensives, L-thyroxine 50 μg daily, linagliptin, insulin, aspirin, atorvastatin, and thiamine. On admission, the TSH was 83 mIU/l, free T4 6.5 pmol/l and free T3 was 1.9 pmol/l; four months earlier, the TSH was 58 mIU/l. He was noted to have staphylococcal septicaemia and acute kidney injury; bacterial endocarditis was excluded. He developed a pruritic, maculo-papular rash that was thought due to dry skin. There was a history of non-compliance with L-thyroxine. Despite increasing the dose to 150 μg od, the TSH continued to rise to >100; the free T4 rose to 14.7, but the fee T3 was 2.0. Over the next two weeks, he became more confused, hypothermic, had a respiratory arrest and was admitted to ITU. Infective and paraneoplastic causes of encephalopathy were excluded. A diagnosis of myxoedema coma was made: L-thyroxine 200 μg was administered daily via a nasogastric tube along with IV liothyronine 10 μg 8-hourly; the total daily dose of hormone was based on weight. IV hydrocortisone was commenced until normal adrenal function was confirmed. TSH was monitored every 48 hours until reduction was noted (it halved every 48 h), then weekly. Improved thyroid function was allied to improvement in consciousness, body temperature, blood pressure and renal function. He was moved to a general ward where he able to make a good recovery, including resolution of his dermopathy. Thyroid hormone replacement was then maintained on L-thyroxine 175 μg od alone. This case illustrates how myxoedema coma may occur following a non-thyroidal illness on a background of hypothyroidism. We believe this was due to reduced conversion of T4 to T3 due to sepsis, leading to myxoedema with reduced absorption of L-thyroxine, setting up a cycle that led to myxoedema coma. This case also illustrates the protean manifestations of severe hypothyroidism. Patients with encephalopathy should be screened for hypothyroidism and thyroid function closely monitored if conscious level deteriorates in patients with pre-existing hypothyroidism.

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P1100

Prevalence of thyroid dysfunction in Catalonia from two different registers: pharmaceutical delivery records and diagnostic records (EUthyroid project)

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Background
Cross-sectional studies performed to estimate the prevalence (Prev) of thyroid dysfunctions are expensive and involve a great effort. Diagnosis and therapeutic prescription records may be a good alternative to monitor such prevalence. They also allow to easily compare the thyroid dysfunctions prevalence of among different populations (EUthyroid Project).
Objective
1) To estimate the Prev of hypothyroidism (hypoT) and hyperthyroidism (hyperT) based on Pharmaceutical Delivery records (PHDR) and on Diagnostic Records (DR) of the population of Catalonia; 2) To analyse the concordance of the results between both registers.
Methods
The population officially insured in the Public Health System (CatSalut) in 2014 was the basis for the calculations of the Prev. The information contained in the PHDR of the CatSalut on the number of DDD dispensed (HO3A: preparations of levothyroxine and HO3B: preparations of antithyroid medication) and the number of patients in treatment (NPT) was used. For the calculation of the prevalence based on the diagnoses, the "Minimum basic data set" registry of CatSalut was used, choosing the ICD-9 codes include 242 code for hyperT and in 244 and 243 codes for hypoT.
Results
The total of Catalan population insured in 2014 (from 0 to 108 years) was 7, 556 330 people. The global Prev of hypoT and hyperT based on NPT with levothyroxine or with antithyroid treatment was 3.07% and 0.14% respectively. The Prev of hypoT estimated by the registered codes 244 + 243 was 2.54%. The prev of hyperT based on the registered code 242 was 0.35%.
Conclusions
The Prev of hypoT is higher based on the PHDR than on the DR. The estimate of hyperT Prev is higher based on DR than on PHDR, probably because the subclinical hyperT is included in DR. Both the DR and the PHDR underestimate the Prev of both diagnoses (HypoT and HyperT) compared to cross-sectional studies of Spain and Catalonia. This discordance might be explained by the difficult record of subclinical dysfunction according to the ICD-9 (and also ICD-10).

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P1101

Dysthyroid optic neuropathy in Grave's disease: two case reports

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Introduction
Ophthalmopathy is the most common extrathyroidal manifestation of Grave's disease, with 3–7% evolving to Dysthyroid Optic Neuropathy (DON), which requires urgent treatment to avoid permanent or progressive visual loss. We describe two cases of DON evaluated at Endocrinology and Metabolism Service of Paraná (SEMPR).
Case 1
Male, 70 years old, previously diagnosed with hypertension, type 2 diabetes with insulin use, microvascular complications and cataracts (corrective surgery 8 years before). Presented with 1 week history of visual loss, conjunctival hyperemia and bilateral periorbital edema to the ophthalmologist, treated with photocoagulation on the left eye for diabetic retinopathy. Progressive visual loss persisted, and the patient was admitted to the hospital for evaluation after NMR of the orbits was compatible with Grave's ophthalmopathy (bilateral periorbital muscle swelling). Endocrinology was consulted and laboratory showed TSH 0.00 mUI/ml (0.35–4.94), free T4 1.8 ng/dl (0.7–1.48), total T3 133.03 ng/dl (58–159) and TRAb 6.66 U/l (< 1.75); clinical evaluation demonstrate a CAS of 6, with visual acuity 20/200 on right eye and 0 on left eye. Pulse therapy with 1 g/d methylprednisolone was initiated, for 3 days, alongside with thiamazole 10mg/day. Patient was discharged for ambulatory treatment with 500mg methylprednisolone per week. Visual acuity improved to 20/60 and 20/160 at 3 g cumulative dose for right and left eye respectively, and 20/60 and 20/40 at 6 g, with a CAS of 3.
Case 2
Women, 44 years old, Grave's disease for 7 years in use of thiamazole 30 mg/day for the past 2 years reached our service with thyrotoxicosis symptoms and progressive visual loss for the past 2 years. Clinical evaluation revealed diffuse goiter, bilateral proptosis of 24 mm, divergent strabismus, CAS 1 (palpebral edema). Laboratory evaluation showed TSH < 0.005 U/l, total T3 133.73 ng/dl and free T4 1.87 ng/dl. Ophthalmology consultation showed reduced visual acuity bilaterally (20/400), lagophthalmos, diffuse keratitis, optic disc hypoplasia and important atrophy of the pigmented cells of retina. Pulse therapy with 1gr methylprednisolone a day was initiated, for 3 days, but without improvement, patient was referred for surgical decompression of the optic nerve. Improvement of the visual acuity was referred by the patient on the second post operatory day.
Conclusion
In order to prevent permanent visual loss, DON must be diagnosed and treated aggressively. Patient 1 showed improvement, but is still on activity, with a planned 8gr of cumulative dosing and reevaluation. Patient 2, probably because of the delay reaching proper treatment, needed decompressive surgery.

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P1102

Conversion from thyroxine-treated autoimmune hypothyroidism to Graves' disease

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Graves' disease (GD) and Hashimoto's thyroiditis (HT) are both autoimmune thyroid diseases. While transition from GD to hypothyroidism has been more frequently reported, conversion of hypothyroidism to GD is uncommon. We describe a series of 3 patients diagnosed with HT and hypothyroidism, treated with L-thyroxine (LT4), who developed persistent hyperthyroidism with increased thyrotropin receptor antibodies (TRAb) levels and, in two of the patients, Graves' ophtalmopathy.
Case 1
A 46 year-old woman with primary hypothyroidism (TSH 169 mIU/l, normal values 0.5–4.5) treated for 3 years with LT4 50 μg/day, develops hyperthyroidism (TSH 0.013 mIU/l, FT4 2.69 pmol/l (0.6–1.76), TPOAb 260 U/ml (0–35), TRAb 27 IU/ml (< 1.75). Although LT4 was reduced and eventually discontinued, the patient developed mild unilateral exophthalmos and diplopia, with a normal-sized highly vascularized thyroid. She was treated with methimazole and i.v. methylprednisolone pulse-therapy. Her TSH level is still suppressed after 5 months.
Case 2
A 54 year-old woman with chronic hepatitis C, treated with pegylated interferon for 3 months, developed overt hypothyroidism with a small diffuse goiter 3 months after IFNα withdrawal (TSH 63.7 mIU/l, FT4 5.38 pmol/ml (10–28.2), TPOAb 3815 U/ml. LT4 was gradually increased up to 100 μg/day. Two months later, despite progressive LT4 withdrawal, the patient developed hyperthyroidism with mild bilateral exophthalmia (TSH < 0.005 mIU/l, FT4 39.6 pmol/l, TPOAb = 434 IU/ml, TRAb 15.5 IU/ml), increased homogenous uptake of ^{99}Tc pertechnetate at thyroid scintigraphy. On methimazole she had rapid oscillations of TSH levels and was treated with radioactive iodine 1 year later.
Case 3
A 39 year-old man with HT, hypothyroidism and intermittent mildly increased calcitonin levels (TSH 12.9 mIU/l, FT4 0.71 ng/dl (0.7–1.48), TPOAb > 1000 U/ml, calcitonin 9.01 pg/ml (1–8.4), with a small micronodular goiter, has been treated with LT4 50 μg/day for 14 months, when he developed progressive hyperthyroidism with increased ^{131}I uptake and TRAb 1.87 IU/ml (< 1.75). He was started on methimazole which normalized TSH levels in 5 months.
Conclusion
Conversion of LT4-treated hypothyroidism to GD is very rare (i.e. three cases in a 20 year- experience of a single clinician). Conversion of blocking- to stimulating-TRAb or distinct immune paradigms for GD and HT may account for this switch, while interferon treatment may be a trigger in some cases.

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P1103

Cholestyramine: a useful therapeutic adjunct in severe thyrotoxicosis

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Case 1
A 32 year old fit and well female presented with symptoms of thyrotoxicosis and goitre. Her initial investigations revealed fT4 45 pmol/l (10–20) and fT3 26 pmol/l (3.5–6.5), with undetectable TSH. TSH receptor antibodies were positive. She was commenced on beta blockers and carbimazole and increased to 60 mg daily, with the fT4 improving only to 34.4 and fT3 to 13.8. Cholestyramine was commenced and titrated to a dose of 4 g twice daily, with resultant normalisation of free thyroid hormones levels. Vitamin D deficiency developed which was treated, but no coagulopathy. Planned thyroidectomy was reconsidered by the patient in view of the clinical response.
Case 2
A 39 year old male gave a history of Graves thyrotoxicosis 4 years earlier for which he was treated with carbimazole for 2 years before defaulting attendance. He represented with severe thyrotoxic symptoms affecting his physical, personal and professional life. Investigations showed fT4 61.6, fT3 29.4, TSH suppressed and TSH receptor antibodies positive. Despite 60 mg of carbimazole daily the fT4 improved only to 37.6 and fT3 to 16.4. Addition of cholestyramine was well tolerated and resulted in further improvements in thyroid hormone levels and considerable symptomatic improvement. Surgery is planned with Lugol's iodine pretreatment.
Discussion
Cholestyramine is a bile acid sequestrant that is predominantly used in the treatment of cholestatic pruritus and dyslipidaemias. The thyrotoxic state leads to an increased enterohepatic circulation, and cholestyramine can bind to thyroid hormones and lead to their increased excretion via the intestinal system. These two cases illustrate its clinical utility as a well tolerated adjunct to thionamides in severe thyrotoxicosis, and its use can buy time for more considered long term management.

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P1104

Elevated level of serum calcitonin of unknown origin

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We describe a case of a 59-years old man, in whom a thyroid nodule with a size of 16 mm and an elevated serum calcitonin level 29 ng/l (upper limit 21 ng/l) was incidentally found. The size of a nodule did not increase in time, serum level of calcitonin was stable and cytology from the nodule was benign. In January 2016, calcium stimulation test was performed with a positive result (baseline calcitonin 31.5 ng/l, stimulated calcitonin 417 ng/l), CEA was low. The patient was refered for thyroidectomy and after the surgery calcitonin level decreased to normal values, calcium test was negative. Histology revealed focal lymphocytic thyroiditis with macrofolicular hyperplastic nodule with regressive changes. Imunohistochemistry detected diffuse and locally nodular hyperplasia of C-cells with a strong expression of calcitonin.
Conclusion
C-cell hyperplasia with an increased secretion of calcitonin is considered to be a preneoplastic lesion associated with a medullary carcinoma of a thyroid gland. Its occurence can be sporadic, or familial in isolated forms or as a part of MEN syndrome. In our case, calcium stimulation test was helpful in differential diagnosis of an elevation of calcitonin of unknown etiology.

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P1105

Prevalence of thyroid nodules in thyrotoxicosis detected in pregnancy

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Introduction
The aim of our study was to evaluate the causes of thyrotoxicosis detected during pregnancy as well as to determine the prevalence of thyroid nodular disease (TND) in our population and which factors are associated with this condition.
Methods
We performed a retrospective review of 1,760 patients between April 2014 and September 2017 remitted from the gynecology department due to thyroid dysfunction detected in the 9th week of pregnancy (universal screening of TSH). Among these patients, 131 presented thyrotoxicosis, defined as TSH <0.13 (reference range of TSH in the first trimester of gestation in our center: 0.13–4.16 mU/l). Patients with known TND ($n=9$), hyperemesis gravidarum ($n=5$) and multiple pregnancy ($n=17$) were excluded. All the patients received iodine supplementation during pregnancy. Thyroid function was evaluated throughout pregnancy and thyroid ultrasound was performed if the TSH remained decreased after the 20th week or if cervical palpation was abnormal. Comparisons within the group were done by T-student test or U-Mann Whitney using STATA program.
Results
Of the 100 patients studied, four were diagnosed with Graves' disease (TRAb-positivity) and 96 with gestational thyrotoxicosis (GT). Among patients with GT, the mean age was 34.3(5.4) years and there were 30 nuliparous (31.2%), 49 uniparous (51.1%) and 17 multiparous (gravidity ≥ 2, 17.7%). The sample consisted predominantly of Caucasians ($n=76$, 79.2%). The level of TSH in the first trimester was undetectable in 55.2% of patients. There was positive thyroid autoimmunity (defined as the presence of TgAb or TPOAb) in 16 patients (16.7%). There were 9 patients (9.4%) who had received treatment with *in vitro* fertilization. In 50 women, thyrotoxicosis was transient (TRAB-negativity, normal TSH $>$ 20th week and normal thyroid palpation). In the other cases ($n=46$), thyroid ultrasound was performed. Thyroid nodules (>2 mm) on ultrasonography were detected in 26 patients, (giving a TND prevalence of 56.5%), with 21 subjects having a nodule >10 mm. Fourteen women had clinically palpable nodules. Women with thyroid nodules were older (36.6 ± 4.9 vs 32.8 ± 5.0 yr, *P*:0.02) and had higher gravidity (*P*:0.04) compared with women having no thyroid nodules. The subject with TND also had higher positive rate of autoimmunity, (26.9% vs 5%, *P*:0.05). No difference in TSH and FT4 was detected throughout pregnancy.
Conclusions
The main cause of hyperthyroidism in pregnant women is gestational thyrotoxicosis. In our population, the prevalence of TND in these women is high, so ultrasound should be considered. TND is associated with older age, greater gravidity and positive autoimmunity.

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P1106

Analysis of association of vitamin D receptor gene Cdx2 (rs11568820) polymorphism with autoimmune thyroid diseases

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Introduction
Vitamin D is postulated to play a significant role in the immune system modulation and its deficiency has been reported in some autoimmune disorders. Polymorphisms of different vitamin D-related genes, among them vitamin D receptor gene (*VDR*), could either be a risk factor for autoimmune diseases. Therefore the aim of the study was to assess the association between *VDR* Cdx2 (rs11568820) polymorphism and autoimmune thyroid disease (AITD) among the Caucasian-Polish population.
Studied group
272 subjects diagnosed with AITD (mean age 50.55) and 119 healthy age and sex matched controls. AITD group comprised of 166 patients with autoimmune thyroiditis (AIT) and 106 patients with thyroid associated orbitopathy (TAO) in the course of Graves' disease. In the control group AITD and other autoimmune diseases or neoplasms were excluded.
Methods
Cdx2 polymorphism genotyping was performed with the use of real-time PCR with TaqMan probes, randomly selected samples were additionally analyzed by direct sequencing. The statistical significance of differences in allele and genotype distribution between AITD and controls, as well as in subgroups of AITD were evaluated by χ^2 or Fisher's exact test, where appropriate. A *P* value of <0.05 was considered significant.

Results
Observed allele frequencies were in Hardy-Weinberg equilibrium, except of TAO subgroup. In both AITD and the control group G allele and GG homozygote predominated, as expected for Caucasian population. The observed allele and genotype frequencies did not differ significantly between AITD and controls ($P=0.30$ and $P=0.56$, respectively). When analyzing AIT vs. controls, differences in allele or genotype distribution were also not significant ($P=0.41$ and $P=0.54$, respectively). In TAO group frequency of genotype AA was higher comparing to controls (6.60% vs. 1.68%), but without statistical significance ($P=0.09$; OR $=4.14$; 95% CI: 0.89–19.96). We also analyzed TAO vs. AIT and found significantly higher AA homozygote in TAO group comparing to AIT (6.60% vs. 1.20%; $P=0.03$; OR $=5.80$; 95% CI: 1.25–27.9).
Conclusions
There is no statistically significant difference in allele or genotype distribution of *VDR* Cdx2 polymorphism between AITD and the control group and between AIT or TAO and the control group among the Caucasian-Polish population. However, we found that TAO patients differed significantly from AIT group in *VDR* Cdx2 genotype distribution.

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P1107

A case of severe hypothyroidism, correcting to euthyroidism through Graves' disease associated with refractory thyroid eye disease

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A 54-year-old female presented to the neurologist in December 2017 with neuromuscular right arm weakness, lethargy and fascial swelling. She had a normal MRI head before being referred to the endocrine clinic with a TSH >125 mIU/l (0.27–4.2 mIU/l). Free T4 was 0.3 pmol/l (12.0–22.0) with a free T3 of <0.4 pmol/l (3.1–6.8). The thyroglobulin antibody was 1366 IU/ml (0–115) with a normal thyroid peroxidase level (TPO) 29.7 (0–34). No previous thyroid disease or a preceding viral illness and no thyroid eye signs. A thyroid ultrasound scan showed features consistent with autoimmune thyroiditis. She was diagnosed with primary autoimmune hypothyroidism and treated with levothyroxine 100 mcg daily with resolution of her neuromuscular weakness. She was discharged in June 2016. She presented in June 2017 to the ophthalmologist with a 3-month history of periorbital oedema. She had a TSH$<$ 0.01, free T3 10.03, free T4 36, TPO 13.25, TG Ab 3508 and a TSH receptor antibody >40 (0–0.8) IU/l indicative of Graves' disease. Levothyroxine was stopped and a thyroid ultrasound scan showed the thyroid gland was markedly heterogeneous with a mildly increased doppler vascularity. A technetium scan showed increased uptake (1.7%) in the right thyroid lobe relative to the left (0.8%). The patient was clinically euthyroid with some mild periorbital oedema. Carbimazole 5 mg was commenced in view of the suppressed TSH and an MRI of the orbits showed diffuse enlargement of extraocular muscles with bilateral proptosis, compatible with thyroid ophthalmopathy. Her thyroid eye disease was refractory to IV methylprednisolone 4.5 g over a period of 12 weeks. She proceeded to radiotherapy with some initial response and may require orbital decompression. At present, she remains off Carbimazole and levothyroxine (TSH 4.14, free T3 3.3, free T4 10.6, TG Ab 913).

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P1108

Changes of visfatin/NAMPT serum concentration and its leukocyte expression in hyperthyroidism

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Purpose
The aim of the study was to investigate changes of visfatin/NAMPT serum concentration and its leukocyte expression in hyperthyroid patients.
Material and methods
The study was designed as a single-center, cross-sectional with consecutive enrollment. We included all patients with newly diagnosed overt hyperthyroidism (Graves' disease or toxic nodular goiter). Each subject underwent physical examination, laboratory investigation, body composition analysis, and thyroid ultrasound. *NAMPT* mRNA leukocyte expressions were measured using RT-qPCR.
Results
Initially, 173 patients were eligible for the study, and due to exclusion criteria 95 were enrolled in further analysis (67 patients with Graves' disease (GD) and 28 with toxic nodular goiter (TNG)). Forty three healthy volunteers adjusted for age, sex and BMI served as a control group. We found higher NAMPT/visfatin serum concentration in patients with GD than in patients with TNG ($P=0.03855$). *NAMPT* leukocyte expression was significantly higher in GD patients ($n=32$) as compared to TNG patients ($n=18$) and euthyroid controls ($n=24$)($P=0.005965$). Simple linear regression analysis revealed that NAMPT/visfatin serum concentration was significantly associated with *NAMPT* leukocyte expression, thyroid autoimmunity, age, HOMA-IR, and fat mass percentage (FM%). *NAMPT* leukocyte expression was associated with thyroid autoimmunity, age, and TRAb levels. The stepwise multiple regression analysis confirmed FM%, HOMA-IR as independent predictors of visfatin/NAMPT serum levels. In a separate stepwise e multiple regression analysis, we confirmed the association between *NAMPT* leukocyte expression and TRAb levels.
Conclusions
We found that visfatin/NAMPT serum elevation in hyperthyroid patients is related to fat mass percentage together with HOMA-IR. Observed *NAMPT* leukocyte overexpression in GD patients and its association with TRAb levels suggest potential involvement of visfatin/NAMPT in pathogenesis of thyroid autoimmunity.

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P1109

Congenital hypothyroidism: genes involved in organogenesis disorders

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Introduction
Congenital hypothyroidism (CH) is the most common congenital endocrine disease since it affects 1/3000–1/4000 births. The involvement of genetics is no longer discussed and several genes have been implied in the different clinical forms of thyroid dysgenesis.
Patients and methods
We report ten cases of thyroid dysgenesis collected at the pediatric and endocrinology departments of Sfax in Tunisia. The diagnosis was based on clinical, biological, morphological investigations of the thyroid gland. To investigate genetic abnormalities involved in the onset of CH in Tunisian families, first, we investigated the case of non-syndromic CH, by looking for mutations in the TSHR gene. Then we look for correlation genotype – phenotype for this gene and other genes involved thyroid development.
Results
Our study consisted of six girls and four boys of 22 months average age at the time of diagnosis. Parental consanguinity was noted in 80%. Three cases of familial form were recored with an autosomal recessive mode of transmission for two and autosomal dominant for the remaining case. The signs of dysthyroidism and delayed stature were the main circumstances of discovery. The non-syndromic form was the most common form. The syndromic associations noticed in the remaining cases were renal impairment, facial dysmorphism. Biologically, thyroid status confirmed peripheral hypothyroidism in all cases. At the end of this assessment, five of our patients had hypoplasia suggestive of TSH resistance syndrome. A mutation of the TSHR is evoked for four4 of these patients. However the molecular analysis TSHR revealed a known polymorphism (c.561T> C (rs 2075179) in exon 7 of the TSHR gene in a homozygous state in a patient with CH and in a heterozygous state in a another patient. No mutation was revealed at that time and the study of other exons is still being analyzed. For the remaining case, resistance to TSH due to Gs protein deficiency was strongly suspected in the presence of pseudohyperparathyroidism. For the three cases of ectopia, the NKx2-5 and TTF-2 genes can be incriminated. A mutation of the PAX8 gene is strongly suspected in association with a renal

anomaly in one case. For the facial dysmorphism noticed in one case, we will complete with FISH study in search of microdeletion7q11.23.
Conclusion
In this work, we have illustrated the contribution of molecular diagnosis of thyroid dysgenesis to establish adequate genetic counseling for families at risk in the lack of systematic neonatal screening.
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P1110

Technique of recurrent laryngeal nerve liberation for phonation recovery
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Background
Recurrent laryngeal nerve (RLN) injury is a major complication in thyroid surgery. It occurs more frequent during operations and reoperations of thyroid cancer and recurrent goiter. Techniques of nerve liberation and reconstruction can provide improvement in phonation, even complete voice recovery. The aim of this study was to analyze usefulness of the RLN liberation technique through level of improvement of symptoms after reoperation on patients who had injury of RLN during previous surgery.
Methods
From 2000 to 2017, we performed reoperations for RLN liberations in 18 patients who had RLN paresis/paralysis on laryngoscopy after initial surgical treatment. Reoperations were performed 2 months to 16 years after RLN injury. The *original Dzodic's technique* (first reported in 2008, published in *World J Surg in 2016*) consists of removing misplaced ligations, granulomas or adhesions from nerves, with its preservation. We use intraoperative neuromonitoring to asses RLN function intraoperatively. After surgery, voice quality was assessed by qualitative scoring system and laryngoscopy in 1st, 6th and 12th postoperative month.
Results
Majority of patients had oncological indication for reoperation. Six patients had reoperation for alleviating the symptoms of severe dysphonia or stridorous breathing. In two patients that had bilateral RLN paralysis and high risk for urgent tracheostoma, we performed a two-step surgery: 2 and 6 months after injury. RLN liberations provided complete voice recovery within 3 weeks in all patients. In 15 patients, score 4 on perceptual voice quality scale was achieved. Three patients, who had RLN liberation 6 months, 3 years and 16 years after the injury, restored normal vocal cord movements on laryngoscopy (score 5). One of them had injury of the non-recurrent laryngeal nerve.
Conclusion
The *original Dzodic's technique of RLN liberation* enables patients with paresis/paralysis due to surgical RLN injury a significant improvement in phonation, even complete voice recovery.
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P1111

Intrathyroidal cyst with squamous metaplasia
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The occurence of multiple squamous cells in thyroid fine needle aspirate is rare.
Aim
We report a case of multiple squamous cells in thyroid aspiration specimen in a patient with chronic lymphocytic thyroiditis.
Case report
A 56-year-old woman has been observed for several years because of chronic lymphocytic thyroiditis and hypothyroidism. She was on levothyroxine supstitution therapy. Six years ago ultrasonography revealed inhomogeneous thyroid, predominantly hypoechogenic with hypoechogenic nodule, measuring 15 mm in diameter, in the right lobe close to isthmus. The FNAC of that nodule revealed chronic lymphocytic thyroiditis. Four months ago we performed control ultrasonography: hypoechogenic, cystic nodule in the right lobe close to isthmus measured 8×9×8 mm. A sonographically guided fine-needle aspiration yielded 1 ml of yellowish material and cytological analysis revealed multiple squamous cells, colloid, macrophages single and in clusters.
Conclusion
Our opinion is that multiple squamous cells in this case originated from metaplasia and degeneration, because fine needle aspiration 6 years ago of the same nodule revealed only chronic lymphocytic thyroiditis.
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P1112

Levothyroxine absorption test: a safe help for difficult cases
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Levothyroxine (L-T4) is the mainstay of treatment of hypothyroidism. Marked elevation of thyrotropin (TSH) in patients on high replacement doses is rare and can result from malabsorption, drug interaction or poor compliance. The levothyroxine absorption test is required to distinguish these causes and has proved to be safe. This test measures the serum free thyroxine (FT4) response to 1 mg of oral L-T4 over 4–24 h.
Clinical cases
Case no 1: A 28-year-old woman presented with congenital primary hypothyroidism, being supplemented since the neonatal period. She has no other relevant medical history and denies additional medications. Review of old records revealed marked elevation of TSH despite L-T4 supplementation at progressively higher doses. In October 2017 she had TSH 182 μUl/ml while taking 112 mcg daily of L-T4 (1.5 mcg/kg). The patient reported taking L-T4 every morning in the fasting state. We performed the L-T4 absorption test with 1 mg of L-T4: TSH 33,3 μUl/ml and FT4 1,01 ng/dl at baseline; TSH 32,1 μUl/ml and FT4 2,12 ng/dl after 4 h. This result confirmed the diagnosis of non-adherence.
Case no 2: A 36-year-old woman with primary hypothyroidism (antibody-negative thyroiditis) presented with uncontrolled hypothyroidism. She has history of Sjogren's syndrome. Medications in addition to L-T4 include hydroxychloroquine, methotrexate and folic acid. In December 2017 she had TSH 58.5 μUl/ml while taking 375 mcg daily of L-T4 (5.3 mcg/kg). She reports taking the levothyroxine regularly in the fasting state. The possibility of a malabsorption state was considered. Autoimmunity for celiac disease was normal, but gastric parietal cell antibodies were positive. Vitamin B12 levels were normal. Although it is recognised that there may be an increased need for L-T4 in patients with atrophic gastritis, this patient is already taking a very high dose. We are going to perform a L-T4 absorption test to exclude non-adherence.
Conclusion
The levothyroxine absorption test allows to distinguish between malabsorption and non-adherence. This test may be particularly useful in cases where malabsorption and noncompliance are likely to explain the failure of therapy. Testing over 4 h offers a safe alternative to longer protocols.
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P1113

Pasireotide and Graves' orbitopathy: outcome in terms of efficacy compared to parenteral metilprednisolone; a pilot study
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Objective
Graves' orbitopathy (GO) is an autoimmune disease that affects about 25% of the patients with Graves' disease. The thyrotropin receptor (TSHR) is the main autoantigen of GO. Somatostatin receptors (SSR) are expressed by orbital fibroblasts (OB) of GO patients. Pasireotide (SOM230) is a somatostatin analog that has a great affinity for the type 1 and type 5 SSRs and inhibits both orbital human lymphocyte and OB proliferation in vitro. Therefore it is interesting to investigate the effect of SOM230 on predefined endpoints in patients with active moderate to severe GO (MSGO).

Methods
This pilot study evaluated 10 patients with active MSGO treated with SOM230 compared to 10 patients with MSGO treated with methylprednisolone (MPNS). They received 4500 mg of intravenous MPNS or 180 mcg of SOM230 for 12 weeks. Clinial endpoints and quality of life (GOQUOL) were evaluated at time 0 and at 12 weeks. GO activity scored by clinical activity score (CAS) was evaluated at time 0, after they received about half of SOM230 or MPNS total dose and at 12 weeks.
Results
The efficacy of SOM230 and MPNS was similar accordig to overall clinical criteria evaluation and GOQUOL: in both groups 50% and 60% of patients improved respectively. Eyelid aperture improved in the SOM230 group compared to the MPNS group althougth not significantly: $-0.7(-2–4.5)$ vs. $-0.15(-3–2)$, $P=0.7$. Hertel absolute decrement was not different in the MPNS group compared with the SOM230 group: 0.75 ± 0.8 vs 0.67 ± 0.7, $P=0.7$, Hertel improved in 3(30%) patients of MNPS group, no patients improved in SOM230 group according to a single point clinical evaluation. CAS absolute decrement at 12 weeks was not different between the groups: -2 (3.2) vs -2 (1.2), $P=0.6$.
Conclusions
SOM230 showed to be as effective as MPNS to improve GO clinical signs and symptoms in MSGO patients when evaluated by overall clinical criteria.

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P1114

Prediabetes and cardiovascular risk factors in patients with autoimmune thyroiditis

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Introduction
Thyroid hormones modulate the insulin sensitivity and glucose metabolism. The interrelation between thyroid autoimmunity, thyroid function, glucose metabolism and cardiovascular risk factors remains uncertain.
Methods
We recorded thyroid function tests, BMI, IR markers comprising the Homeostasis Model Assessment for insulin resistance (HOMA-IR and HOMA-B), the Quantitative Insulin Sensitivity Check Index (QUICKI), HISI (Hepatic Insulin Sensitivity Index), WBISI (Whole-Body Insulin Sensitivity Index), IGI (Insulinogenic Index) and the levels of total cholesterol (TC), HDL, LDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB), ApoA1, lipoprotein (a) (Lp[a]), homocysteine, CRP (C-reactive protein), folic acid and vitamin B12 levels, in 354 patients with AIT, 93.5% woman, with a mean age of 46.0 ± 15.5 years. A 75-g OGTT was performed and measurements of plasma glucose, insulin, and C-peptide were obtained. Statistical analysis was performed with the Mann-Whitney test and the Spearman's correlations test. A two-tailed $P\leq0.05$ was considered significant.
Results
After dividing the OGTT sample in 3 groups (IFG-16.6%, IGT- 24.2% and diabetes DM-9.6%), we found that patients with IFG had significantly higher levels than IGT patients in homocysteine (9.50 ± 2.09 vs 7.24 ± 1.33 µmol/l; $P=0.002$) and HOMA-IR (3.86 ± 2.76 vs 2.14 ± 1.00; $P=0.01$). The levels of CRP were significantly higher among patients with prediabetes comparing with normoglycemic patients (0.552 ± 1.053 vs 0.346 ± 0.467 mg/dl, $P=0.003$). In patients with prediabetes, we found lower levels of HISI (120.63 ± 289.16 vs 59.00 ± 65.91, $P<0.001$) and WBISI (7.30 ± 5.66 vs 4.06 ± 2.67, $P<0.001$), and higher levels of IGI (0.57 ± 0.38 vs 1.16 ± 0.77, $P<0.001$). Patients with prediabetes presented higher levels of TC (211 ± 49 mg/dl vs 196 ± 35 mg/dl, $P=0.016$) and LDL (133 ± 37 mg/dl vs 120 ± 28 mg/dl, $P=0.002$). In the whole sample we observed significant correlations between TSH and insulin ($r=0.20$; $P=0.02$), total cholesterol ($r=0.10$, $P=0.04$) and apoB ($r=0.18$, $P=0.02$). In the IFG group we found significant correlations between FT3 and TC ($r=-0.53$; $P=0.01$), LDL ($r=-0.57$; $P=0.006$) and ApoB ($r=-0.53$; $P=0.03$). In IGT group we detected correlations between insulin and CRP ($r=0.61$; $P=0.002$), and between homocysteine and anti-TPO antibodies ($r=0.46$; $P=0.02$).
Conclusions
In patients with AIT, the presence of prediabetes is associated with higher cardiovascular risk. The screening of prediabetes with OGTT may be important in this group of patients to stratify the cardiovascular risk.

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P1115

The significance of rare genetic variants in the thyroid autoimmunity – brief review and our own results on *SLC26A4* variants in Hashimoto's thyroiditis

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Identified genetic players for most common diseases are not sufficient to explain their heritability. This situation is known as the missing heritability problem. One among the possible explanations is the impact of rare variants. We present our own results of rare variants in the gene *SLC26A4* in Hashimoto's thyroiditis (HT), which were not found in controls, and therefore confirm the possibility of their impact on this disease. We genotyped 147 Hashimoto's thyroiditis cases (10.2% men) and 147 controls (13.6% men) matched for age, gender, marital status, education, monthly income, and size of the city they live in. The gene *SLC26A4* encoding for a iodine transporter was Sanger-sequenced in 20 HT cases, in order to identify new rare variants in this gene. We identified 2 new variants, which have not been previously reported. Two among the investigated SNPs were not differentially represented in both groups: c.-103T>C, previously associated with Pendred syndrome, and c.1708-18T>A, previously proven as benign. In contrast, variants located in the coding region, which have previously been assigned as benign or likely benign. Those included p.Ser190Arg ($n=4$ cases), p.Ile300Leu ($n=3$), p.Phe354Ser ($n=3$), p.Ala456Ala ($n=2$), p.Leu597Ser ($n=4$), p.Val609Gly ($n=2$) and p.Asp772Tyr ($n=1$). It seems very probable that rare variants are at least one of the reasons for missing heritability. It seems possible that the variants we identified in HT may play a joint role in HT, as most of them co-occurred in the same patients. Future studies should target genome-wide rare variants, as probably different genes will have a combined role in the risk of those diseases.

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P1116

High dose metformin in obese PCOS patients with subclinical hypothyroidism

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Background
Polycystic ovarian syndrome (PCOS) diagnosis is set based on Rotterdam criteria, including hyperandrogenism, chronic anovulation and typical ultrasound appearance. 65–70% of women with PCOS have insulin resistance. Metformin, an oral antidiabetic agent, was the first drug used to treat insulin resistance in PCOS patients.
Material and method
Twenty non-diabetic women between 25–35 years old, with PCOS untreated prior to presentation, with a BMI >30 kg/m^2, were included in our study. Ovarian, thyroid ultrasound, BMI, TSH, fT4 levels were evaluated at baseline, at 3 and 6 months of treatement. All patients received metformin administered daily on a weekly increased dose up from 500 mg/day to a total of 2 g/day. 9 patients had subclinical hypothyroidism (SCH) (TSH levels 4.5–6 mUI/l). 11 patients were euthyroid. None of the patients had received levothyroxine treatment before the inclusion in our study. None of the patients were on a meat and dairy free diet.
Results
TSH levels decreased from a median of 4.9 mUI/ml at baseline to a 2.8 mUI/l after 3 month of treatment. Levothyroxine was added after 3 months of treatement in 4 of the patients (TSH >4.5 mUI/l). At 6 months all SCH patients had normal TSH levels (<3.1 mUI/l). No significant changes in TSH levels were noticed in euthyroid patients.

Conclusions
Metformin use induced an TSH lowering effect in obese patients with PCOS and SCH, reducing the need for levothyroxine replacement in selected patients.
Keywords: metformin, pcos, subclinical hypothyroidism.
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P1117

Selenium supplementation and progression of Graves orbitopathy

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Selenium (Se) is a micronutrient of vital importance to human health. It acts as an antioxidant, immunomodulator and also it is involved in the control of specific endocrine pathways. In adults, the thyroid is the organ with the highest amount of selenium per gram of tissue. The literature suggests that selenium supplementation of patients with Hashimotos thyroiditis is associated with a reduction in antithyroperoxidase antibody levels. Selenium supplementation also in mild Graves orbitopathy is associated with delayed progression of ocular disorders. The aim of this work is to evaluate the effect of selenium supplementation on progression of Graves Orbitopathy.
Design
An open-label, randomized controlled study was performed in 40 Graves-Basedows disease patients with mild form of Graves orbitopathy (GO) divided in to two groups: 1) Selenium group patients ($n=18$) received methimazole and selenium 200 ug for 6 months and 2) Control group patients ($n=22$) received methimazole alone for 6 months. Methimazole was discontinued at 24 weeks in euthyroid patients.
Results
After six months of treatment 12 of 18 (66.6%) in selenium group and 7 of 22 (31.8%) had no progression of orbitopathy (OR 1.18; $P<0.05$). Serum levels of free triiodothyronine/free tetraiodothyronine, thyroid-stimulating hormone receptor antibody, prevalence of moderate to severe Graves orbitopathy, thyroid volume were significantly lower in group treated with selenium than in control group after six months of treatment.
Conclusion
These results indicated that methimazole and selenium combination is more effective in reduction of Graves orbitopathy than the methimazole monotherapy.
Keywords: Graves orbitopathy, Hashimoto thyroiditis, selenium supplementation.
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Thyroid Cancer

P1118

Mixed medullary–papillary carcinoma of the thyroid: a case report

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Introduction
The coexistence of two types of tumors of different origins in the same thyroid is a rare phenomenon. Its etiopathogenesis remains unknown. We report the case of a mixed papillary and medullary carcinoma of the thyroid revealed by a compressive goiter.
Case report
A 70-year old woman with a history of right lobo-isthmusectomy for a toxic solitary adenoma, presented 30 years later with a chief complaint of a cervical mass accompanied by difficulty in swallowing. Her family history was free of any endocrine or non-endocrine malignant tumors. On physical examination, she had a left thyroid nodule of 4 cm in the greatest dimension without palpable cervical lymph nodes. Laboratory tests indicated hyperthyroidism with a decreased TSH of 0.002 μUI/ml and an increased free T4 of 26.6pmol/l. Thyroid scintigraphy showed a toxic multiheteronodular goiter. Cervico-thoracic CT scan showed an intrathoracic goiter exerting a mass effect on the trachea and the esophagus. The serum calcitonin assay was not performed preoperatively. The patient underwent a left thyroid lobectomy without lymph node dissection. Permanent histopathologic analysis revealed mixed papillary and medullary thyroid carcinoma in a multinodular adenomatous goiter. The immunohistochemical study confirms the histopathological examination by showing a calcitonin and a thyroglobulin staining. The patient was planned for a cervical lymph node dissection followed by a radioiodine therapy.
Conclusion
The simultaneous occurrence of medullary and papillary thyroid cancer is the result of a simple coincidence due to the high frequency of papillary micro carcinomas of the thyroid. This case illustrates the importance of the thyrocalcitonin assay in presence of any thyroid nodule.
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P1119

Epidemiology of thyroid nodules in the United Arab Emirates: five-years tertiary center analysis

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Background
Thyroid malignancy is the sixth common cancer type in the United Arab Emirates (UAE) where its incidence is increasing worldwide. There are no epidemiological data outlining the prevalence of cancer in thyroid nodules, nor previous analysis of ultrasonographic features correlating with thyroid malignancy in the UAE.
Aim
To report the prevalence of thyroid malignancy in thyroid nodules and correlate it with demographic data. A secondary aim is to define some ultrasonographic features that could predict thyroid malignancy.
Methods
Retrospective electronic medical records review of patients with thyroid nodules aged 18–80 years with a normal TSH who underwent ultrasound guided fine needle aspiration biopsy (UG-FNA) at Sheikh Khalifa Medical City (SKMC) during 2011–2015.
Results
A total of 573 nodules with normal Thyroid Stimulating Hormone (TSH) underwent UG-FNA cytological examination. Nodules were more frequent in females (59.2%) between 30–49 years of age and in males, (48.4%) between 40–59 years of age. The overall crude prevalence of thyroid cancer in thyroid nodules was 8.8% (95% Confidence Interval (CI) 6.5%–11.2%). The prevalence was 8.3% (95% CI 5.8–10.8) in females and 11.9% (95% CI 5.0–18.8) in males. The prevalence among UAE nationals, Arabs, and Far East Asians was 8%, 9.5% and 13.3% respectively. Classical papillary thyroid cancer was found in 46.9% of all cancerous nodules. Of all malignant nodules, 36.2% were complex and 36.2% were of hypoechoic echogenicity. 41.7% of cancerous nodules were between 2–4 cm size.
Conclusion
Cancer rate was higher in males (11.9%) compared to that in females (8.3%). Among the heterogenous population in the UAE, East Asians had the highest prevalence malignancy in examined thyroid nosules. The most common histological type is papillary thyroid cancer. Ultrasonographic features associated with malignancy are nodular size between 2–4 cm and echogenicity of either hypoechoic or complex.
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P1120

Thyroid ultrasonographic characteristics and Bethesda results after FNAB

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Objectives
Fine needle aspiration biopsy (FNAB) is the initial investigation of choice for thyroid nodules. The Bethesda System (B) classifies thyroid cytological patterns into six categories (B1-6) according to risk for malignancy.
Methods
A total of 1113 patients (210 males/903 females) underwent FNAB for the same number of thyroid nodules. Their mean age was 56.2 ± 21.6 years $\pm$ S.D. We

correlated the demographic profile (age and gender) and sonographic features of these nodules with the FNAB outcome. The Bethesda system for reporting thyroid cytopathology was used.
Results
Out of total 1113 cases, 255 (22.9%) cases were diagnosed as non diagnostic (B1), 780 (70.1%) were diagnosed as benign (B2), 35 (3.1%) as B3 (atypia/follicular lesion of undetermined significance), 10 (0.9%) as B4 (follicular neoplasm or suspicious for follicular neoplasm), while 13 (1.2%) cases were categorized as B5 (suspicious for malignancy) and 20 (1.8%) as B6 (malignant). Remarkably, 11 nodules of 33 of category B5 and B6 each had a maximum diameter of less that 1 cm. When comparing benign result (B2) vs. result of category B3–6 irregular shape (6.5% in B2 vs. 15.4% in B3–6, $P=0.004$), ill-defined margins of the nodule (10.6% in B2 nodules vs. 20.5% in B3-6 nodules, $P=0.033$), the presence of calcifications (24.2% in B2 nodules vs. 65.4% in B3-6 nodules, $P<0.001$) and the hypoechogenity of nodule (41.9% in B2 vs. 65.4% in B3-6, $P<0.001$) decreased significantly the possibility for benign (B2) result, whereas features such as the size of nodule, the presence of central vascularity, the composition and the heterogeneity of parenchyma did not affect the possibility for B2 vs. B3–6 result ($P>0.05$). Finally, there was no association of gender and age with the Bethesda category result.
Conclusions
Our study supports that the irregular shape of a nodule, ill-defined margins, the presence of calcifications and the hypoechogenenity of a nodule decrease the possibility of a Bethesda benign result. FNAB of nodules <10 mm may reveal suspicious or positive for malignancy cytology.

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P1121

The diagnostic value of elastography score and strain indexfor the evaluation of thyroid micronodules

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Background and aim
In the general population, the frequency of thyroid micronodules is increasing and the prevalence of malignancy is higher in nodules at this size. The ultrasonographic features of these nodules are neither spesific nor sensitive Elastography gives information about the degree of hardness at the tissue level and provides assessment of malignancy risk of the nodule. The aim of the study was to investigate the diagnostic value of elastography in patients with thyroid micronodules.
Methods
Two hundred and twenty-four patients with thyroid micronodules were recruited in this prospective study. All patients underwent a thyroid fine-needle aspiration biopsy (FNAB). Elastography scores and indexes were measured with real-time ultrasound elastography (Preirus HV machine with 13 MHz linear transducer).
Results
The outcome of our study shows that malignant micronodules compared the bening micronodules, malignant micronodules were with higher elastography scores (ES) and strain indexes (SI) values ($P<0.001$). When we use ES to diagnose malignancy that ES is >3 providing 79.4% sensitivity and 98.1% specificity for diagnosing malignancy. The area under the curve (AUC) for the ES was 0.888 ($P<0.001$). The best cut-off point for strain index which differentiates benign from malignant micronodules was 3.06 with 98% sensitivity, 91% specificity. AUC for the SI was 0.970 ($P<0.001$).
Conclusions
Elastography score and strain ratio of the thyroid micronodules are beneficial markers during malignancy investigation. According to our study, the strain index is better than elasto score when assessing the malignancy in thyroid micronodules.

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P1122

Radiofrequency ablation for micropapillary thyroid carcinoma: evaluation of clinical efficacy

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Purpose
Papillary thyroid cancer is the most common type of thyroid carcinoma and represents approximately 80% of all thyroid cancers. The aim of the study is an evaluation of the treatment results of micropapillary thyroid carcinoma by the radiofrequency ablation (RFA).
Materials and methods
Fourteen patients with papillary thyroid carcinoma T1aN0M0 with wild type of BRAF (V600E) were included in this research: 12 women and 2 men. The median age of the group was 36 (24–42). The mean nodule size was 0.7 (0.3–1.0) cm. In 12 cases nodules had solid content, in 1 case – mixed solid and cystic content. The mean duration of RFA was 7 (3–12) min. All the procedures were performed under local anesthesia with real time ultrasound control. Technique of dynamic RFA was applied. Internally cooled 7–10 cm length, 0.5, 0.7, 1.0 cm active tip electrodes were used. During the procedure permanent control of hoarse voice was carried out to avoid complications. The follow-up period of patients was 2–15 months.
Results
An ultrasound was used for evaluation of the efficacy of RFA at the first month of the follow-up. An elevation of echogenicity in the ablation area and the loss of Doppler signals were seen. None of the patients experienced any major complications.
Conclusion
RFA is a minimally invasive technique for treatment of micropapillary thyroid carcinoma with high clinical efficacy.

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P1123

Prevalence and clinical significance of *BRAF*^{V600E} mutation in patients with papillary thyroid cancer

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Background
The *BRAF*^{V600E} mutation is the most common mutation in papillary thyroid carcinoma (PTC). Its presence has been associated with extrathyroid invasion, lymph node metastasis, and tumor recurrence. Recently, assessment of the *BRAF*^{V600E} mutation status in patients with PTC has been used as a method to predict tumor aggressiveness.
Objective
Our aim has been to analyze the prevalence of *BRAF*^{V600E} mutation in a cohort of patients with PTC in our geographical and its relationship with poor prognostic factors or aggressiveness of the disease. We also investigated whether this mutation is related to the persistence of the disease 12 months after initial therapy.
Patients and methods
We retrospectively studied patients older than 18 years who underwent surgery for PTC at our centre from 2011 to 2017. Clinical, analytical, histological and molecular data were obtained from all patients with assessed *BRAF*^{V600E} mutation ($n=159$). In patients with more than 12 months of follow up after initial therapy data on the dynamic risk stratification results were recorded.
Results
The prevalence of *BRAF*^{V600E} mutation was 58.3% (95% confidence interval, 49.6–66.5). No differences in patients classified by gender or age groups were found. We could not find any significant association between *BRAF*^{V600E} mutation status and the evaluated clinical and analytical parameters (including radioiodine remnant ablation and postsurgical serum thyroglobulin levels). Tumor size, multifocal disease, extrathyroidal extension, or the presence of lymph node metastases were not related to the presence or absence of *BRAF*^{V600E} mutation. A significant association between this mutation and the histological variants of PTC was found. *BRAF*^{V600E} mutation was found in 71.4% of patients with the classical variant of PTC and only in 44.2% of those with the follicular variant of PTC ($P=0.002$). Twelve months after initial therapy 66% of our patients showed no evidence of disease according to the criteria of dynamic risk stratification (excellent response). We did not find any relationship between *BRAF*^{V600E} mutation and the persistence or remission of disease at this time.
Conclusion
BRAF^{V600E} mutation is very common (58.3%) in our population of patients with PTC. In this cohort of patients the presence of *BRAF*^{V600E} mutation is related with the histological variant of PTC, but we could not find any significant relationship with other histopathological features or with the response to treatment one year after initial therapy.

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P1124

Association of pro-inflammatory biomarkers in papillary thyroid cancer: a prospective study

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Introduction
Papillary thyroid carcinoma (PTC) is the commonest endocrine malignancy. Apart from genetic role in its pathogenesis, autoimmunity has been implicated in certain papers. But, reports have been tripolar ranging from causative, protective and neutral role of immunomodulation. In this context, we set out study the role of Pro- inflammatory cytokines in PTC in South Indian population.
Material and methods
This prospective case-control study was conducted on surgically managed PTC patients. Institutional ethical committee approval was obtained. Diagnosis of PTC was based on imaging, fine needle aspiration cytology and later confirmed by histopathology. Exclusion criteria were subjects with any systemic or chronic inflammatory disease or any medication which interferes with the normal function of the hypothalamic-pituitary-gonadal axis. Serum samples were collected from 53 PTC subjects and 51 age matched healthy controls. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF-α) and high sensitive C reactive protein (hsCRP), leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.
Results
The mean hSCRP level in PTC and controls were 17.9 ± 3.1 mg/ml and 5.8 ± 1.3 mg/ml respectively. The mean TNF-α level, IL-6 level and Leptin levels were 294 ± 33 pg/ml, 13.9 ± 4.7 pg/ml and 1.9 ± 0.8 ng/ml respectively. Serum leptin level in controls was 3.4 ± 1.6 ng/ml. There was statistically significant difference of all the pro-inflammatory cytokines compared to controls (P value < 0.05) with negative correlation for leptin levels.
Conclusions
This study shows raised titers of pro-inflammatory markers – IL-6, TNF-α and hsCRP, while reduced leptin levels correlated with PTC suggesting a contributory role. But, the exact immuno-modulatory role and pathogenetic mechanism needs more investigational research.

Keywords: Papillary thyroid cancer, Tumour necrosis factor, Interleukin-6, Goiter, Auto-immunity, Leptin
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P1125

An unusual association of three endocrine diseases: pheochromocytoma, hyperparathyroidism and papillary thyroid carcinoma

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Introduction
Pheochromocytoma, papillary thyroid carcinoma and primary hyperparathyroidism have been reported rarely together. Whether the association is coincidental or results from an underlying unique genetic process is difficult to ascertain.
Case description
We report a case of a 59-year-old woman without a family history who had a personal history of multinodular goiter known for the ten last years and pheochromocytoma diagnosed and operated in 2008. In 2015 thyroid scintigraphy reveals a cold nodule in the left lobe. Fine needle aspiration shows benign follicular lesion. Calcitonin and thyroid function were normal. In addition, blood tests revealed hypercalcemia secondary to primary hyperparathyroidism. Due to tracheal compression seen on a neck CT-Scan, she underwent total thyroidectomy and intraoperative parathyroid exploration. Pathological examination showed bilateral papillary carcinoma in follicular presentation with vascular invasion and parathyroid gland hyperplasia. Tumor cells were negative for calcitonin and CEA. The patient was screened for germline variants for several candidate genes: RET (exons 8, 10, 11, 13, 14, 15 and 16), VHL, SDHB, SDHC, SDHD, SDHA. This search did not show any mutation. The genetic study by "Next Generation Sequencing" searching for 50 genes linked to cancer was performed in the thyroid tumour. There was a mutation in the HRAS gene (mutation pG13R in exon 2).
Conclusions
This is the rare reported case of the unusual combination of pheochromocytoma, bilateral papillary thyroid carcinoma and primary hyperparathyroidism with parathyroid gland hyperplasia**.** The genetic abnormality of this rare association needs further studies but may lie in the HRAS gene although a coincidental association cannot be excluded.

Keywords: pheochromocytoma, primary hyperparathyroidism and papillary thyroid carcinoma
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P1126

Coexistence of well differentiated, poorlydifferentiated and anaplastic thyroid carcinoma in a male patient with neurofibromas: A case report

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Introduction
Poorly differentiated thyroid carcinoma (PDTC) and anaplastic thyroid carcinoma (ATC) have been conjectured to arise from well differentiated thyroid carcinoma (WDTC) due to frequently reported synchronous and metachronous occurrence. We demonstrate the simultaneous presence of divergent histological subtypes in a single thyroid gland, with escalating loss of p53 expression in more aggressive variants.
Material and methods
A 60-year-old male with multiple neurofibromas presented with a palpable anterior neck mass, firm and fixed to underlying structures. Hormonal evaluation was conducted to evaluate thyroid function and rule out the presence of a pheochromocytoma, on grounds of unproven von Recklinghausen disease. Ultrasound revealed a hypoechogenic nodule on the left lobe, measuring 5.84×2.81 cm, with peripheral vascularity, which comprised a 2.24×1.28 cm area with suspicious calcifications. Three smaller hypoechogenic nodules with peripheral vascularity, 3.26, 3.18 and 0.83 cm respectively, were also observed. On the right lobe three isoechogenic nodules, 2.19, 1.47 and 0.73 cm, with cystic areas and no remarkable vascularity were noted.
Results
Histopathological examination revealed three foci at the right lobe, with characteristics of predominantly papillary but also follicular carcinoma growth pattern, with infiltrating margins and foci of extrathyroidal extension. At the left lobe two lesions were described, which presented with histologic features of insular and trabecular variant of PDTC. The larger tumor showed foci of anaplastic transition, with diffuse growth pattern, nuclear pleomorphism and areas of necrosis. Both tumors invaded thyroid capsule and displayed extrathyroidal extension reaching the inked surgical margins. Vascular emboli were also identified. Poorly differentiated tumor area appeared with reduced nuclear p53 protein accumulation.
Conclusion
We present a case of progressive decline of p53 expression in multifocal thyroid tumor areas consisting of WDTC, PDTC and ATC histologies, highlighting the possibility that WDTC can progress to PDTC and then ATC through an intricate procedure involving loss of p53.

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P1127

Incidence of recurrent nerve paresis and hypocalcemia after total thyroidectomy – A retrospective Analysis

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The aim of this study was to investigate: the incidence of postoperative paresis of the recurrent laryngeal nerve (RLN) and hypocalcemia; the frequency of incidental parathyroidectomy and the occurrence of hypocalcemia, and to find possible risk factors for hypocalcemia and RLN paresis.
Material and methods
Retrospective analysis of 550 patients after total thyroidectomy (TT) or completion thyroidectomy (CT) after histologically confirmed thyroid carcinoma. Postoperative RLN paresis was determined by postoperative laryngoscopy, and the index of recurrent injury (IRI) was calculated. Patients were monitored for postoperative clinical and biochemical hypocalcemia. Total calcium levels in plasma $<$ 2.0 mmol/l were regarded as hypocalcemia. Incidental parathyroidectomy (IPT) was identified by histology.
Results
Postoperative unilateral RLN paresis occurred in 15 patients (2.7%), of which 4 cases were permanent (0.7%), and IRI was 8. Postoperative transient hypocalcemia was observed in 32 (5.8%) and permanent hypocalcemia in 2 patients (0.3%). The occurrence of RLN pareses and incidence of hypocalcemia was significantly higher in patients with malignant tumors than in benign lesions: 7.1% vs. 1.6% RR = 4.47; 95% CI: 1.66–12.06; (P = 0.004) and 9.8% vs. 4.8% RR = 2.05; 95% CI: 1.00–4.12 (P = 0.041), respectively. IPT was reported in 67 patients (12.2%). IPT/ non IPT and CT/TT patients had significantly higher incidence of transient hypocalcemia 13.4% vs. 5.2% RR = 2.82; 95% CI 1.36–5.84 (P = 0.015) and 27.3% vs. 5.8% RR = 5.69; 95%CI: 1.58–20.48 (P = 0.025), respectively.
Conclusion
Risk factors of transient hypocalcemia and unilateral RLN paresis were thyroid malignancies, extend of lymph node dissection, surgical technique and mainly the surgeon's experience. Incidental parathyroidectomy and completion thyroidectomy significantly correlated with transient hypocalcemia. A higher frequency of incidental parathyroidectomy was observed in patients younger ($\leq$45 years).
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P1128

Highly sensitive Thyroglobulin assay in monitoring patients treated for differentiated thyoid cancer in 26 consecutive patients
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Introduction
Guidelines suggest that serum basal (nonstimulated) thyroblobulin (bTg) with sensitive assays (Functional Sensitivity-FS- below 0.1 or 0.2 ng/ml) could substitute the measurement of serum Tg levels after TSH stimulation during the follow-up of patients with differentiated thyroid cancer (DTC) when basal results fall below the FS.
Objective
A sensitive assay for Tg was incorporate in our center (Chemiluminiscent Tg Access; Beckam Coulter; Brea; CA) with FS of 0.1 ng/ml coexisting with an older traditional assay (Inmunoradiometric SelcoTg assay; Berlin) with higher FS (0.5 ng/ml). The aim of this study was to verify that sensitive bTg values below FS could obviate the need of stimulation with recombinant (rTSH) in patients consecutively seen for the follow-up of CDT in one endocrinology office between January and June 2017.
Patients and methods
Patients with DTC from one endocrinology office were included if:
– They underwent total thyroidectomy usually followed by 131 iodide ablation.
– They had a recent documented bTg determined with the sensitive assay (provided that Tg antibodies were negative) and a recent stimulated Tg (sTg) after rTSH administration determined with the IRMA assay.

Patients were classified in 3 categories:
– Excellent treatment responders: no clinical, biochemical or structural evidence of disease and sTg (IRMA method) below 1 ng/ml.
– Patients with structural disease cytologically or hystologically evidentiated.
– Incomplete biochemical responders: sTg above 1 ng/ml (IRMA method) in the absence of localizable disease.

Results
Study included 26 patients (4 men), mean age (DS): 49(15) years with DTC treated with total thyroidectomy (some of them with central and lateral neck dissection) followed by an ^{131}Iodide ablative dose in 25 cases. 4 patients had been reoperated and 3 received a second ^{131} Iodide dose because of recurrent nodal disease. Among Excellent treatment responders (n = 21), bTg was lower than 0.1 ng/ml in all but one case (0.2 ng/ml). In the case with structural disease (metastatic nodal recurrence) bTg raised above FS level (3.4 ng/ml). Among Incomplete biochemical responders (n = 4), 3 had bTg $>$ 0.1 ng/ml and that one with bTg $<$ 0.1 ng/ml had a marginally sTg (1.2 ng/dl) with the traditional assay of doubtful clinical significance.
Conclusion
Sensitive Tg methods could obviate the need for sTg in a majority of DTC patients and therefore could simplify the follow-up and alleviate the costs of rTSH.
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P1129

Hounsfield unit value has null effect on thyroid nodules at 18F-FDG PET/CT scans
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Objectives
Detection rate of thyroid nodules is increasing with use of new imaging modalities, like 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT). To avoid unnecessary operations, differentiating between benign and malignant 18F-FDG PET/CT-positive thyroid nodules is essential. Many authorities recommend fine needle aspiration biopsy (FNAB) for exclusion of malignancy in thyroid nodules. Although FNAB is a simple, easily performed procedure, less invasive diagnostic approaches are required. Malignant thyroid nodules tend to have higher maximum standardized uptake values (SUVmax) but there is no clear information about the utility of Hounsfield Unit (HU) values for the prediction of malignancy. This study evaluated the HU values beside SUVmax for detecting malignancy risk of PET/CT-positive thyroid nodules.
Methods
We retrospectively studied 98 patients who had FNAB for thyroid nodules detected on PET/CT within the period; January 2011 to December 2015. The FNABs and surgical pathological results were recorded. On non-contrast CT scans taken during PET imaging, the HU of the nodules were calculated besides SUV max values of the nodules.
Results
The mean age of the study population was 57.6 $\pm$ 13.8 years, and 75 (76.5%) of the patients were women. The most common primary malignancy detected in these patients was breast cancer. If more than one nodule was detected on a PET/CT scan, FNAB was performed on the nodule that had the higher $SUV_{max.}$ FNABs revealed benign results in 32 patients (32.7%), malignant in 18 (18.4%), non-diagnostic in 20 (20.4%), indeterminate in 28 (28.5%). 24 patients underwent thyroidectomy due to their inconvenient general health conditions. When the FNAB and postoperative pathological results of nodules evaluated together, 38 of them were considered as benign and 25 of them were malignant. Only 24.5% of the cases were subjected to thyroidectomy, the malignancy rate was 25.5% in our cohort. Mean SUVmax was significantly higher ($P <$ 0.001) in malignant versus benign nodules. Area under curve (AUC) was 0.824 for SUVmax; the cut-off value was over 5.55 ($P <$ 0.001), with 80% sensitivity, 84.5% specificity. But mean HU values were not significantly different (P = 0.73).
Conclusions
We defined a SUVmax cut-off value of 5.5 for malignant potential of thyroid nodules detected on PET/CT. However; we did not find any merit in using HU values for discriminating between malignant and benign nodules.
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P1130

Follicular thyroid carcinoma with late metastasis to kidney in a patient with elevated thyroglobulin levels of unknown source
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Here we present a case of follicular thyroid cancer with elevation of thyroglobulin (Tg, in ng/ml) detected almost 10 years after initial surgery and radioactive iodine therapy (RAI). The elevated Tg persisted for years before he was found to have a metastasis in his kidney 16 years after his initial cancer treatment. A 78 year old male had a total thyroidectomy followed by RAI therapy in 2001 for a 2.4 cm

follicular thyroid cancer. His Tg became mildly elevated in 2009, and continued to rise gradually. Body scan, PET scan and neck ultrasound did not find a source for the Tg. In 12/12 his Tg was 49.4 with a suppressed TSH. A thyrogen stimulated Tg in 2/13 was 930 and again ultrasound, body scan and PET scan were unremarkable. He was treated empirically with 210 mCi 131-I. His Tg level came down and remained <2 but a thyrogen stimulated Tg was 8.8 in 10/14. Tg antibodies have always been undetectable. Tg continued to rise to 96.5 on levothyroxine in 6/15. Again ultrasound, body scan and PET scan were unremarkable. On an abdominal CT scan for appendicitis in 10/15 a 1.4 cm right renal lesion was observed which remained stable on active surveillance. An increase in size of the renal mass was noted in Sept 2017 leading to radical nephrectomy. The pathology of the right kidney showed a lobulated $2.7\times2.4\times2.0$ cm mass, and histologic appearance and immunostains led to diagnosis of metastatic thyroid follicular carcinoma. Tg in 3/17 on levothyroxine was 63.4, and rose to 95.4 in 6/17, 267.5 in 9/17 and 190.9 in 10/17 before his nephrectomy. Interestingly, the presence and change in the renal mass corresponded to his Tg levels all along. In retrospect the small renal mass could be seen on his PET CT films from 2012. The increased FDG uptake in the kidney appears to have been missed due to normal FDG uptake in the urinary tract. At the time of his last body scan in 2015 the renal mass was only 1.4 cm on CT and likely below the detection of the 131-I. A Tg level after kidney surgery is 1.1 Conclusion: Given the rarity of thyroid cancer metastases to the kidney, and the uptake of FDG in the urinary tract, a renal metastasis may be missed during evaluation of patients with persistent elevations of thyroglobulin.

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P1131

The role of platelet activation and inflammation in patients with differentiated thyroid cancer

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Background
The role of inflammation in the pathogenesis of cancer and the mechanisms through which platelets can influence the aggressive behaviour of different types of cancer have been highlighted by a few studies.
Methods
We retrospectively analysed the files of 493 patients submitted to thyroidectomy in our surgery department between 2012 and 2015. We assessed the relationship between differentiated thyroid cancer (DTC) and mean platelet volume (MPV), platelet count and serum fibrinogen level in a case-control study.
Results
The study included 86 patients with DTC (mean age 53.99 ± 13.91 years, 83.7% females) and a control group of 66 patients with histologic benign thyroid disorders (mean age 50.14 ± 13.05 years, 83.3% females). Patients with DTC had a higher level of serum fibrinogen compared to patients in the control group ($P=0.033$). We did not find any significant differences between case and control groups regarding MPV ($P=0.150$) or platelet count ($P=0.342$) levels. MPV was not significantly different between histologycal subgroups of DTC patients depending on: TNM staging ($P=0.308$), tumor subtype ($P=0.108$), vascular invasion ($P=0.829$), capsular invasion ($P=0.357$), extracapsular extension ($P=0.161$), local lymph nodes metastasis ($P=0.362$). In DTC patients, the platelet count was higher in patients with higher tumour diameters ($P=0.024$) and capsular invasion ($P=0.044$). In DTC patients platelet count was significantly lower after the surgery compared to preoperatory values ($P=0.050$).
Conclusions
Our data showed that, when compared to benign thyroid disorders, DTC was associated with a higher level of inflammation. In DTC patients, platelet count can be associated with aggressive tumor behaviour.

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P1132

Incidental thyroid microcarcinoma in benign thyroid diseases: can it encourage total thyroidectomy as the first choice of surgical treatment? (A retrospective study)

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Aim
Well-differentiated thyroid cancer (TC) comprises the most common endocrine malignancy, featuring very good prognosis and 5-year survival rate of nearly 100% after total thyroidectomy. However, the prevalence of incidental thyroid microcarcinoma (mITC) is continuously rising during the last decade. One obvious reason is the high prevalence of total thyroidectomy (TT) as the preferred operation for otherwise benign nodular or diffuse thyroid diseases. The current retrospective study aims to evaluate the prevalence of mITC (max. diam. ≤1 cm) in benign thyroid diseases as a potential parameter for surgical decision regarding the type of thyroidectomy.
Patients-methods
In one Surgical Department, with specialty interest in Neck Endocrine Surgery, a cohort of 793 patients (660 females/133 males; mean age 51,1 years), underwent TT for benign thyroid diseases, during 13 years (1.1.2004-31.12.2016). All patients were referred for surgical treatment from MDs of Internal Medicine or Endocrinology. Patients with positive/suspicious or non-inclusive cytology, or history of TC, were excluded. Pathological report of mITC was recorded and evaluated according to preoperative diagnosis.
Results
The prevalence of mITC was 14.5% (115/793 patients: females/males: 88/27), while 678 patients (85.5%) were free of malignancy. Evaluation regarding the type of thyroid disease revealed that a percentage of 32.3% (40/124 patients) with solitary thyroid nodule-STN and another of 12.8% (68/530 patients) with multinodular goiter-MNG, were harboring an incidentally detected TC. Thyroid diseases with hyperthyroidism, such as Graves' disease and toxic multinodular goiter featured malignancy in 8.1% (3/37 patients) and 4.6% (4/87 patients) respectively. Interestingly, mITC was diagnosed in 15.4% (2/13 patients) with previous thyroid lobectomy or subtotal thyroidectomy; among them there was a case of mITC with foci of anaplastic TC.
Conclusions
Incidental thyroid microcarcinoma was identified in a significant proportion of patients with otherwise benign thyroid diseases subjected to TT. The vast majority presented in non-toxic disorders, while mITC was detected in nearly 1/6 of patients with nodular recurrence after previous non-total thyroidectomy. These findings can support the choice of TT as the optimal surgical procedure even in benign thyroid diseases with indication for surgery. Moreover, the first choice of TT leads simultaneously to permanent cure of a potential concomitant thyroid carcinoma, excluding the possibility of future neck re-operation and/or complex longtime follow-up.

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P1133

Incidental thyroid microcarcinoma diagnosed after total thyroidectomy for non-toxic solitary thyroid nodule: A 13-year single surgical-center experience (A retrospective study)

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Aim
Thyroid cancer (TC) is the most common endocrine malignancy, presenting a rising incidence during the last decade, due to continuously rising prevalence of incidental thyroid microcarcinomas (mITCs; ≤1 cm) in benign thyroid diseases treated with total thyroidectomy (TT). Solitary thyroid nodule (STN) is a thyroid condition, which remains under debate regarding the extent of thyroidectomy

needed (total or near-total thyroidectomy vs unilateral lobectomy). Objective of the current retrospective study was the assessment of the prevalence of mITC in patients with non-toxic STN subjected to TT, within a time period of 13 years.
Patients-methods
In one Surgical Department, with specialty interest in Neck Endocrine Surgery, a total of 124 patients (90 females/34 males; mean age 47.1 years), underwent TT for solitary thyroid nodule, from 2004 to 2016. Type of thyroidectomy is a choice of the surgical team. All patients were referred for surgical treatment from MDs of Internal Medicine or Endocrinology. Patients with positive/suspicious or non-inclusive cytology, or history of TC, were excluded. Pathological report of mITC was recorded and evaluated according to location of nodule and special features of detected TC.
Results
The prevalence of mITC was 32.3% (40/124 patients), while 84 patients were free of malignancy. Specifically, in 72.5% (29/40 patients) a papillary mITC was diagnosed, while the other types of thyroid carcinoma were: 15% (6/40 patients) follicular mITC, 5% (2/40 patients) papillary + follicular mITC, 5% (2/40 patients) medullary mITC and 2.5% (1/40 patients) foci of anaplastic TC. Interestingly, the case of anaplastic mITC referred to recurrent STN in the remnant lobe after previous lobectomy. Regarding the location and type of pathologically detected mITC, in 7.5% (3/40 patients; 2 papillary/1 papillary + follicular TC), there was multifocal carcinoma in both thyroid lobes. Surprisingly, in 22.5% (9/40 patients; 8 papillary/1 follicular TC) the malignancy was contralateral to STN.
Conclusions
Incidental thyroid microcarcinoma was identified in a significant proportion, nearly 1/3, of patients with solitary thyroid nodule, subjected to total thyroidectomy. More than 1/5 of patients featured mITC at the contralateral lobe. Although the small number of study group comprises a limitation, findings can support the choice of total thyroidectomy as a safe procedure in STN, giving the advantage of treating the disease and also diminishing the possibility of non-detected thyroid cancer or disease recurrence and need for neck re-exploration

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P1134

The relationship between clinical, morphological and prognostic characteristics of papillary thyroid carcinoma with *BRAFV600E* mutation assessed immunohistochemically

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Background
Papillary thyroid carcinoma (PTC), especially its classic papillary, oncocytic, Warthin-like, tall and columnar cell variants, is characterized by a high frequency of BRAFV600E mutation that varies in different studies from 36 to 85%. Prognostic significance of the mutation remains controversial.
Objective
Aim of the study was an analysis of relationship between clinical, morphological and prognostic characteristics of PTC with BRAFV600E assessed immunohistochemically.
Material and methods
Histological and immunohistochemical study of formalin-fixed paraffin-embedded sections of primary, metastatic and recurrent (if available) PTC was conducted with mouse monoclonal antibodies to protein products of mutated BRAF in 74 patients (18 males and 56 females aged from 9 to 80 years. at the time of first operation). Results of immunohistochemistry were scored by three pathologists, and agreed opinion was considered for analysis of relationship between BRAF mutational status and clinical, morphological and prognostic features of PTC.
Results
Mutant BRAF status was observed in 29 of 74 PTC (39%). BRAF positive group of PTC was characterized by higher proportion of male patients (37.9 vs 15.5%, $P=0.050$), older age at the time of operation (39.3 vs 28.4 years., $P=0.005$), and higher frequency of advanced clinical stages (37.9 vs 13.3%, $P=0.023$). Classic papillary histotype of PTC was diagnosed more often (65.5 vs 35.5%, $P=0.017$), and frequency of tumor post-operational relapses was higher (62.1 vs 33.3%, $P=0.018$) in BRAF positive group in comparison with BRAF negative. BRAF negative group displayed a higher frequency of distant metastases, the volume of surgical operation was generally larger. No significant difference with regard to BRAF status was found for pT, pN categories, extrathyroidal tumor extension, multifocality, and encapsulation. Analysis of disease-free survival based on multivariate proportional hazard models demonstrated significantly elevated rate of relapse in the BRAF positive group, and that BRAF mutation was a prognostic factor of time-related tumor relapse independent from the extent of surgery.
Conclusions
The BRAF mutation is an important risk factor for PTC relapse that may be useful for prognostication during post-operational follow up.

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P1135

Improved prognostic value of the eighth edition of the AJCC/TNM staging system for differentiated thyroid cancer

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Background
In January 2018, the 8th edition of the AJCC/TNM staging system for differentiated thyroid cancer (DTC) was introduced in clinical practice. Studies evaluating this 8th edition so far only comprised patients with papillary thyroid cancer (PTC) or made no distinction between PTC and follicular thyroid cancer (FTC). Therefore, we evaluated the prognostic value of the AJCC/TNM 8th edition in a European population with DTC, and subsequently distinguished PTC and FTC patients.
Methods
Adult patients diagnosed and/or treated for DTC at the Erasmus MC between January 2002 and April 2016 were included. For both editions, overall survival (OS) and disease specific survival (DSS) were analyzed using the Kaplan-Meier (KM) method. The Cox proportional hazards model was used to compare the effect of PTC and FTC on survival. The statistical model performance of the 7th and 8th edition was assessed using the C-index, AIC and BIC.
Results
We included 792 patients (69% women) with DTC (79% PTC, 21% FTC). Mean age was 49 years and median follow-up 86 months. Reclassification with the 8th edition resulted in down-staging of 282 (36%) patients, an increased number of patients in stage I (431 to 575) and II (82 to 129), and an equivalent decrease in stage III (96 to 30) and IV (183 to 58). For DTC, as well as for PTC and FTC separately, stage at diagnosis was significantly related to both OS and DSS ($P<0.001$) in the 7th and 8th edition. However, examination of the KM survival curves showed better separation of the stage curves for the 8th than for the 7th edition. In contrast with the 7th, no significant differences regarding survival rates per stage between PTC and FTC were seen using the 8th edition. Furthermore, the statistical model performance was better for the 8th than for the 7th edition.
Conclusion
We showed that the 8th edition of the AJCC/TNM staging system is a better predictor for both OS and DSS than the previous 7th edition in a European population of patients with PTC or FTC. Furthermore, differences in survival rates between PTC and FTC that were present using the 7th edition disappeared using the 8th edition, implicating that this new edition is predicting well regardless of DTC subtype.

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P1136

Quantitative asessments of normal cervical lymph nodes using shear-wave ultrasound elastography

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Purpose
The aim of this study was to evaluate the reference values of quantitative shear wave elastography (SWE) for cervical lymph nodes with normal ultrasound

characteristics, and assess if there are differences according the location and other characteristics of patients.
Methods
67 cervical lymph nodes from 52 patients with thyroid nodules that were diagnosed previously as different thyroid disease had been imaged with SWE. The shear elasticity modulus, which indicates the stiffness of the lymph nodes, was measured in transverse position in three locations from medial to distal and in longitudinal position from cranial to caudal also in three locations on each lymph nodes, both the second measure corresponds the location of hilum.
Results
All the lymph nodes fulfilled all the ultrasound characteristics of benignity. Mean transverse value of elasticity of the lymph nodes were significantly different ($P=0.005$) by location (II: 20.97 KPa; III: 18.09; IV: 16.41 KPa; V: 26.99 KPa). The longitudinal mean measure was significantly higher than the transversal mean measure (29.58 KPa vs 15.39 KPa; $P=0.013$). There were no differences by measurements from the medial to the distal or from the cranial to the caudal. Also, no difference by volume, diagnosis, age or gender.
Conclusions
SWE may be valuable quantitative indicators for characterizing cervical lymph nodes, but there are differences by location of lymph node and the position of ultrasound probe that need to be standardized.

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P1137

ABO blood groups, Rh factor and thyroid cancer risk: To 'B' or not to 'B'

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Aim
In this study, we aimed to evaluate ABO blood groups and Rh factor in patients with thyroid cancer. We also assessed whether the ABO/Rh factor had any effect on prognosis, agressive features and advanced stage of thyroid malignancies.
Methods
Medical records of patients who underwent thyroidectomy between December 2006 and September 2014 were evaluated retrospectively. Demographical and clinical features, cytological results (according to Bethesda classification), ABO blood groups and Rh factor status of patients with benign and malignant thyroid disease were compared. Additionaly, in malignant group, histopathological features were compared in patients with different ABO blood groups, and Rh positive and negative patients.
Results
Histopathological diagnosis was benign in 1299 (63.5%) and malignant in 744 (36.5%) patients. There were no significant difference in age, sex, thyroid autoantibody positivity and ABO blood groups in benign and malignant patients ($P>0.05$ for each). Ratio of Rh positive patients was significantly higher in malignant compared to benign group (91.8% vs 88.1%, $P<0.046$). In all subgroups of cytology, malignancy rates were similar in different ABO blood groups, and Rh positive and negative patients. Considering malignant patients, extrathyroidal extension and advanced stage (3–4) were more prevalant in patients with B compared to non-B blood groups ($P=0.028$ and $P=0.042$, respectively). Patients with O blood group had lower rate of capsular invasion than patients with non-O blood groups ($P=0.018$). ABO blood groups or Rh status were not associated with thyroid cancer in this study. However, patients with B blood group had higher risk of extrathyroidal extension and advanced stage compared to patients with non-B blood group.
Conclusion
For the first time in our study, we evaluted the association of Rh factor status and thyroid cancer, and found no significant relation. ABO blood groups also did not increase malignancy risk in thyroid nodules. In malignant patients, extrathyroidal extension and advanced stage were higher in B compared to non-B blood groups. Our findings can be considered as a preliminary to investigate ABO blood groups and Rh status as factors that can identify patients with higher risk.

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P1138

A case of anaplastic thyroid carcinoma complicated with thyrotoxicosis

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Background
Anaplastic thyroid carcinoma (ATC), which is one of the most aggressive endocrine tumors. Primary thyroid carcinoma typically does not interfere with thyroid function and presentation of ATC with thyrotoxic state is extremely rare. We present here an ATC patient who is complicated with thyrotoxicosis.
Case
A 69-year-old man presented with neck swelling and pointed out thyroid tumor with calcification two years ago. He appeared general fatigue, body weight loss and palpitation with elevated thyroid hormone, therefore he was transferred to our hospital for further examinations. Laboratory data showed thyrotoxicosis (TSH <0.05 μIU/ml, fT_3 5.5 pg/ml, fT_4 2.3 ng/dl) with negative TSH receptor antibody (TRAb <0.7 U/l), and a low grade uptake of ^{123}I scintigraphy in thyroid gland (0.2%). Ultrasonography showed diffuse goiter with low-echo levels and a 2.4 cm tumor with eggshell-like calcification at right lobe. Spontaneous remission was observed in thyrotoxicosis and it was consistent with destructive thyroiditis. One month later, he complained back pain and rib bone destruction was pointed out. Diffuse goiter was enlarged and diagnosed as ATC according to histological examination (TTF1 positive, p53 positive, MIB-1 index 30%). FDG-PET showed abnormal accumulation in thyroid, lung, bone and adrenals, which corresponded with multiple metastasis of ATC (Stage IVC). Multi-kinase inhibitor (Lenvatinib) was prescribed as treatment of ATC and RANKL inhibitor (Denosumab) was used against bone metastatic regions. However, these treatments were not effective and he moved to palliative care.
Conclusion
Thyrotoxicosis in ATC is very rare and only ten cases have been reported previously. Several explanations have been discussed in this phenomenon, and a representative theory is thyroid hormone leakage due to rapid tissue destruction, which is considered as same mechanisms in the present case.

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P1139

Tyrosine kinase inhibitor (TKI) treatment outcome of stage IV-C thyroid differentiated cancer (analyzed by lesion evaluation)

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Introduction
The standard treatment for differentiated thyroid carcinoma (DTC) with distant metastasis comprises complete total thyroidectomy and lymph node dissection, followed by radioactive iodine (RAI) ablation for metastatic lesions. However, between 2014 and 2015, sorafenib and lenvatinib have been approved for treatment of RAI-refractory advanced thyroid cancer in Japan. We retrospectively analyzed how the treatment results have changed after the approval of tyrosine kinase inhibitor (TKI) treatment.
Patients and methods
Among patients currently followed at outpatient clinics, 111 diagnosed with stage IV-C DTC who underwent surgery at our hospitals were included. A total of 48 patients with disease progression and an estimated lesion size ≥ 15 mm were treated with sorafenib and/or lenvatinib. The approval rate was 43.2%. Lesion evaluation was performed to compare and study these prognoses among 21 patients with lung metastasis, 18 with unresectable local recurrence, and nine with bone metastasis.
Results
Treatment results were classified as partial response (PR), stable disease (SD), not evaluable, and progressive disease (PD) in 16 (33.3%), 18 (37.5%), five (10.4%), and nine (18.8%) patients, respectively. The disease control rate (PR + SD) was 34/48 (70.8%) patients. Lesion evaluation showed that the disease control rate for pulmonary metastasis was the best (81.0%) and for bone metastasis (66.7%) and unresectable local recurrence (61.1%) was the worst (Table 1).
Conclusion
Because disease progression of pulmonary metastasis can be identified on a computed tomography image, the timing of TKI treatment was easy to determine

and the treatment outcome was satisfactory. However, in some cases, local recurrence involved large blood vessels, or therapy was interrupted due to tumor-skin fistula or bleeding. Eventually, some patients died due to an adverse event (AE) or PD. Some cases of bone metastasis were initially diagnosed with large metastatic lesions, and the treatment outcomes were considered worse. Our results suggested that an appropriate timing of TKI administration and the control of its AEs can improve the prognosis of patients with stage IV-C DTCs with PD.

Table 1

Lesion	N	PR	SD	NE	PD	Death
Pulmonary	21	10	7	2	2	4
Local rec.	18	6	5	3	4	6
Bone	9	0	6	0	3	4
Total	48	16	18	5	9	14

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P1140

Expression of VEGFR2 and clinical response of anaplastic thyroid cancer to lenvatinib

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Introduction
Angiogenesis is known to play an important role in the development, growth, and metastasis of carcinomas. The vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) are major molecules involved in angiogenesis. The VEGF family includes seven members, respectively named VEGF-A (often simply denoted as VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor. The VEGFR is a tyrosine kinase receptor with one to three types and is activated by binding to the VEGF. Among these receptors, the VEGFR2 has an important role in angiogenesis. It is suggested that the expression of VEGF correlates with advanced tumor stage in papillary thyroid cancer (PTC). Anaplastic thyroid cancer (ATC) accounts for 2% of all thyroid cancers but is one of the most lethal neoplasms in humans, with a median survival of 4–6 months. Conventional ATC therapy uses a multimodal approach with radiation therapy and conventional chemotherapy. Some patients survive for a fairly long time after receiving this therapy. A monoclonal antibody against VEGF has been developed for cancer treatment, and its antitumor effect has been reported. The effectiveness of lenvatinib, which mainly inhibits the VEGFR2, has been shown for PTC. Lenvatinib also has significant antitumor effects for ATC and is used in clinical practice. However, few studies report the expression of VEGF or VEGFR in ATC. Here, we studied the expression of VEGFR2 in ATC and the therapeutic effect of lenvatinib on ATC.
Materials and methods
Primary tumors were obtained from 12 patients with ATC (five males, seven females; age range, 63–89 years)[Editor1] who underwent surgery or core needle biopsy of a thyroid tumor at the Department of Breast and Endocrine Surgery, Kanagawa Cancer Center, Kanagawa, Japan. The protein expression of VEGFR2 in ATC was analyzed using immunohistochemical analysis. Furthermore, the therapeutic effect of lenvatinib was evaluated in seven patients who underwent the same tissue biopsy and lesion evaluation.
Result
All 12 patients had no expression of VEGFR2. The therapeutic effect of lenvatinib was classified as a partial response in four patients and as a stable disease in three patients.
Conclusion
There was no correlation between the expression of VEGFR2 in ATC tissues and the therapeutic effect of lenvatinib. Further studies are required to improve the overall survival of patients with ATC by investigating clinical predictive factors or new therapeutic target molecules.

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P1141

Medullary thyroid carcinoma: a case report on the efficacy and safety of combined treatment with Vandetanib and Lanreotide Autogel

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Introduction
Treatment options for progressive metastatic unresectable medullary thyroid carcinoma (MTC) include tyrosine kinase inhibitors (TKIs) or somatostatin analogues (SSA), although the efficacy of the latter is debatable. In such cases, combined treatment of TKIs and SSAs has not previously been reported.
Aim
To present a metastatic MTC case successfully treated with a combination of Vandetanib and Lanreotide Autogel.
Case report
A 67-year-old patient presented with progressively exacerbated anorexia, 40 kg weight loss and chronic diarrhoea. Abdominal CT scan demonstrated a hilus hepatic mass of 5.4 cm and multiple hepatic metastases. Hepatic biopsy revealed a well-differentiated neuroendocrine tumour. Octreoscan showed increased uptake in the liver and left thyroid lobe. Neck/chest CT scan revealed a mass of 4.46 cm in the left thyroid lobe. One month later, upon referred to our department, abdomen MRI showed enlargement of the hilus hepatic mass up to 10.5 cm and multiple hepatic metastatic lesions the greater of which 11 cm, located in the right lobe, suggesting rapid progression of the disease. Thyroid FNA confirmed an MTC. Calcitonin (60 300 pg/ml) and CEA (851 μg/l) levels were elevated. Based on hormonal, radiological and cytological findings an unrespectable rapidly progressive metastatic MTC was diagnosed. Given the rapid progression of disease combination treatment with Lanreotide Autogel 120 mg s.c. monthly and Vandetanib 300 mg daily was initiated, hoping to hamper further progression. In view of the possible synergic action of the above-mentioned drugs on QTc prolongation, the patient was kept under close electrocardiographic monitoring. No signs of QTc prolongation were marked. The patient experienced rapid remission of the diarrhoeic syndrome and shrinkage of the thyroid mass, which became almost impalpable within 4 weeks. Six months later, a new Abdomen MRI and neck/chest CT showed a significant shrinkage in size and number of the above-mentioned lesions. No new lesions were observed. The majority of hepatic metastases was non-measurable, the metastatic hilum mass became 4.5 cm and the thyroid mass 2.9 cm. Overall tumour burden reduced $>30\%$ according to RECIST criteria. Calcitonin levels fell to 125 pg/ml, while CEA unexpectedly elevated to 1528.5 μg/l, regardless of clinical and radiological remission. No adverse effects requiring dose adjustment were observed.
Conclusions
Combination of Vandetanib and Lanreotide Autogel could be considered as a safe and effective treatment for metastatic, rapidly progressive, unresectable MTC. Further studies comparing combination treatment to Vandetanib monotherapy are needed to validate the efficacy of this approach.

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P1142

Increased incidence of thyroid cancer in a spanish tertiary hospital, valladolid, spain: evolution and clinical characteristics, 2002–2016

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Introduction
Thyroid cancer is the most frequent malignant endocrine neoplasia. Its incidence has significantly risen worldwide in the last decades.
Objective
To estimate the incidence of thyroid cancer in Valladolid's east area population, Spain, over the period 2002–2016.

Methods
A retrospective descriptive research was performed in the Clinical Universitary Hospital of Valladolid (HCUVa). Clinical data was obtained from Anatomical Pathology Registry of HCUVa from 2002 to 2016. At diagnosis, the age, sex, histological features, size and stage of the thyroid tumor were analyzed. Incidence diagnosed rates were calculated adjusted to reference European Population by sex and age in three-year periods.
Results
398 patients were diagnosed of Differentiated Thyroid Cancer from 2002 to 2016; 78.6% were women with a mean age of 52.44 years (DS 15.20). The overall incidence of thyroid cancer increased over the last 15 years, from 5.2 to 25.7 per 10^5 population/year in women and from 2.3 to 8.8 per 10^5 population/year in men ($P<0.0001$). Incidence rates were significantly higher in males compared to females. Mean age at diagnosis increased from 45.54 years (DS 15.94) to 54.53 years (DS 15.61) ($P<0.01$). There were no statistical differences in tumor size at diagnosis. However, a size increment trend in papillary macrocarcinomas from 1.8 cm (DS 0.77) to 2.49 cm (DS 1.54) – ns – was observed. Gender and papillary and follicular carcinoma rates kept stable over the period (19.2–21.4%) and (92.3–97.1% and 7.7–3.3%), respectively -ns-. An increase in micropapillary thyroid cancer (<1 cm) from 29.4% to 52.1% -ns- was observed throughout the period. Finally, the distribution of papillary carcinomas over the whole period was: 51.21% of classic variant of papillary thyroid cancer, 42.98% of follicular variant and 5.8% of aggressive variant. An increment of follicular variant and aggressive papillary carcinoma from 29.2% to 50.7% and from 4.2% to 8.2% was observed from 2002 to 2016, respectively ($P<0.05$).
Conclusions
During the period studied, the incidence of thyroid cancer increased in Valladolid in both sexes. The increase in micropapillary thyroid cancer diagnose was mainly responsible for this rising trend. These results suggest an increase of thyroid cancer in the diagnosis due to changes in clinical practice and the extensive introduction of new diagnostic techniques, such as neck ultrasonography.

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P1143

The significance of postoperative calcitonin (CT) levels in the evaluation of disease course in medullary thyroid cancer (MTC) patients

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Aim
Postoperative calcitonin (postCT) is a prognostic factor for disease progression in MTC patients. We evaluated the disease course in patients with persistently elevated post-CT.
Methods
Of all MTC patients ($n=273$) followed-up in our Unit (for 1–37, median 7 years), 140 (39.3% men, 67.1% sporadicMTCs) had persistently elevated postCT (≥2.0 pg/ml). Clinical and biochemical data were recorded. Patients were classified in four groups according to postCT: group1: (2–12 pg/ml, $n=34$, 24.3%), group 2: (13–50 pg/ml, $n=26$, 18.6%), group 3: (51–200 pg/ml, $n=30$, 21.4%), group 4: (>200 pg/ml, $n=50$, 35.7%).
Results
Men had post-CT>50 ($P=0.005$) more frequently. SporadicMTCs had post-CT>200 more frequently than familialMTC (43.6% vs 19.6%,$P=0.019$). With increasing postCT, unfavorable histopathological features and multiple surgeries ($n\geq2$) were more frequent ($P<0.001$), tumor size was larger (median (IQR) 1.0(1.8), 1.25(1.23), 1.5(0.9), 2.5(1.8) cm, $P<0.001$) and preoperative-CT was higher (200(334), 17.9(732), 455(1011), 2500 (>10.000), $P=0.002$) in the four groups respectively. Distant metastases at diagnosis were present only in group4 patients (31.3%, all with post-CT>400). Metastatic disease appeared in 8% of group 1, 8% of group 2, 29.6% of group 3 and 68.9% of group four during follow up; progression was recorded in 5.9%, 19.2%, 26.7% and 78.0% while disease remission at last follow-up (after multiple interventions) was recorded in 71.0%, 27.3%, 14.3% και 0.0%, in the four groups respectively ($P<0.001$). The 10-year probability of absence of disease progression differed significantly between the four groups (group1: 94.1%, group 2: 80.8%, group 3: 73.3%, group 4: 22%, $\chi^2=30.3$, $P<0.001$ Log Rank). In Cox-proportional hazard analysis when age, sex, histological features, disease stage at diagnosis and postCT group were taken into account, the only predictor for disease progression were postCT ($P=0.037$), familial disease ($P=0.016$) and stage ($P=0.05$).
Conclusions
This study confirms that postCT are significant predictors of the clinical course in MTC patients. Approximately 20% of patients with postCT>200 showed slow disease progression. Increased awareness is required for patients with low-CT-secreting MTC as their levels may not reflect the disease extent.

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P1144

Changing treatment trends with radioiodine in thyroid carcinoma at the beginning of 21st century in Castilla-La Mancha (Spain)

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Background and objective
The incidence of differentiated thyroid carcinoma (DTC) is increasing worldwide. Radioiodine (RAI) ablation is one of the main elements in the therapy of DTC after surgical removal of the gland. This study aims to compare the use of I131 in a Spanish Cohort of DTC before and after the American Thyroid Association (ATA) 2009 guidelines.
Patients and methods
The Cadit-CAM study was designed to evaluate retrospectively characteristics of patients diagnosed of DTC in Castilla-La Mancha (CAM), a region in the central part of Spain, from 2001 to 2015. The cohort in Cadit-CAM study included 1434 patients from seven hospitals. We studied the use of RAI ablation therapy n this cohort. Patient recurrence risk was assessed using ATA risk stratification system (Low, Intermediate and High risk).
Results
1426 patients were analyzed (77% women, 92% papillary carcinomas). 1183 of them received RAI ablation (83.4%). The mean initial activity of I131 was 101.3 mCi. The mean accumulated activity was 148.7 mCi, only 21.7% of the patients received more than one RAI ablation therapy. Before 2010, RAI was used in 565 of 639 patients (88.4%). Between 2010 and 2015, 618 of the 779 patients diagnosed with DTC received RAI ablation therapy (79.3%, $P<0.01$). 81.1% of patients in the Low Risk category received I131 before 2010 and after this year only 66.5% were submitted to RAI ($P<0.01$). In Intermediate and High risk patients there were no differences in RAI therapy (99.0% vs 97.8% and 98.3% vs 90.7%, respectively) between the two periods. In microcarcinomas I131 was used in 65.9% before 2010 and in 46.7% after ($P<0.01$). Mean initial activity in low risk patients was significantly different before and after 2010 (99.3 vs 68.9 mCi, $P<0.01$). The recurrence rate of microcarcinomas and low-risk DTC was less than 1.5% in patients without RAI therapy in this Spanish Cohort.
Conclusion
There is a trend in using less RAI ablation in low-risk DTC after the 2009 ATA guidelines. In our cohort the prognosis of microcarcinoma and low-risk DTC was excellent in patients treated and not treated with RAI ablation therapy. We recommend risk-based selection of patients candidates for RAI, according to international guidelines.

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P1145

Chronic lymphocytic thyroiditis is associated with decreased staging of differentiated thyroid cancer

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Introduction
Despite numerous studies, the biological association between chronic lymphocytic thyroiditis (CLT) and differentiated thyroid cancer (DTC) has not been elucidated yet. The aim of the study was to assess whether the presence of CLT exerts any influence on clinical or histological presentation of DTC.
Materials and methods
Complete medical records of 907 consecutive patients with DTC treated at a single tertiary care department of endocrinology in the years 1998–2016 were subjected for analysis. The patients were divided into two groups according to the presence (studied group) or absence (control group) of concomitant CLT. Particular parameters were evaluated and compared between the groups. The statistical differences were analysed.
Results
Out of 907 patients included in the study, 331 were diagnosed with DTC and CLT (studied group) while 576 patients with DTC but without CLT constituted a control group. There was no difference in the distribution of papillary and follicular thyroid cancer in both groups. Patients from the studied group were younger than controls at the moment of diagnosis. The prevalence of pT1 was greater than for pT2-pT4 DTC ($P=0.0003$; OR = 1.69, range: 1.27–2.24) in the studied group compared to controls (68.3% vs 56.1% respectively). The thyroid capsule infiltration without extrathyroidal invasion was more frequent ($P<0.0001$) and post-thyroidectomy TgAb levels were greater ($P<0.0001$) but Tg levels were lower ($P<0.0001$) in the studied group. The presence of multifocal lesions was similar in both groups. Multivariate regression analysis confirmed that the protective factors against higher tumour staging (pT2-pT4) were female sex, papillary, unlike follicular, thyroid cancer and the co-occurrence of CLT.
Conclusions
The collected data indicate a protective role of CLT in preventing spread of the DTC. The presence of CLT might possibly limit tumour growth to primary site.

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P1146

Clinical characteristics and prognostic factors in patients with follicular thyroid carcinoma

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Objective
The aim of this study is to evaluate clinical characteristics of patients diagnosed of follicular thyroid carcinoma and to study factors that are associated with a worse prognosis of the disease.
Methods
We included 153 patients diagnosed of follicular thyroid carcinoma in our centre between January 1985 and December 2016. The baseline characteristics of the patients, and their long-term outcomes were collected. The mean follow-up was 15.2 years.
Results
The mean age of the patients was 45.6 ± 15.2 years and we found a higher prevalence of women (79.1%, $n=121$). The mean tumor size was 36.3 ± 17.8 mm. According to the AJCC/TNM classification, we observed 94 patients (61.4%) in stage I, 36 patients (23.5%) in stage II, 18 patients (11.8%) in stage III and three patients (2%) in stage IV. There was a higher prevalence of minimally invasive tumors (84.3% vs. 15.7%). In the follow-up, 3.9% of the patients died due to the tumor or had recurrence or persistence of the disease at the end of the study. In the univariate analysis the presence of persistence/recurrence or death was associated with an increased age, TNM classification at diagnosis and histological subtype (minimally or widely invasive). Using a multivariate model (logistic regression) only the histological subtype was associated with a worse tumor prognosis ($P=0.041$).
Conclusion
- In our study, the 10 years disease-free survival rate of patients diagnosed of follicular thyroid carcinoma was 96.4%.
- The most important predictor of persistence/recurrence of the disease or mortality was the histological subtype.
- The 10 years disease-free survival of widely invasive tumor was 80.2%

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P1147

Association between Hashimoto's thyroiditis and thyroid lymphoma

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Introduction
Lymphoma usually occurs within lymph nodes, but in rare cases, it arises from lymphocytes that are presented within the thyroid gland**.** Thyroid lymphoma is rare, representing less than 5% of thyroid malignancies and less than 2% of all lymphomas occurring outside of the lymph nodes and it is more likely to occur in people with Hashimoto's thyroiditis. In this case we present a patient with Hashimoto's thyroiditis (HT) and thyroid lymphoma (TL).
Case
63 years women presented to the outpatients clinic with complains of fatigue, weakness of voice and enlargement of the neck. She has autoimmune thyroiditis (anti-TPO 53 kU/l) for 10 years. She has been taking Levothyroxin 50 μg per day for 5 years. Few weeks ago, she had noticed painless fast swelling left side of the neck and after 2 weeks the enlargement of the right side of the neck. Physical examination showed a large palpable mass on the both sides of the neck and an enlarged thyroid. Laboratory studies showed elevated sedimetation rate 34 mm/h (normal <13 mm/h), elevated anti-TPO antibodies 689kU/l (0–12) and anti-Tg 682 kU/l (0–100). Other laboratory measurements, including haemoglobin and leukocytes, thyroid hormones (FT4 15.22 pmol/l (12–22), TSH 0.72 mU/l (0.27–4.2), anti-TSH-R 3U/l (<9)), calcitonin <0.42 pmol/l (0–2.8), were normal. In the thyroid ultrasound examination thyroid enlarged, hypoechoic, heterogeneous, in the left side pathological lymph nodes – suspicion of lymphoma or anaplastic carcinoma. Other radiological tests, including abdomen ultrasound, chest X-ray and mammography, evaluating the spread of oncological process, were normal. Core needle biopsy of the thyroid was taken and showed a Diffuse large B-cell lymphoma (DLBCL). PET-CT scan showed metabolically active lymphoproliferative process in the thyroid, in the lymph nodes of mediastinum, in the small intestine and in the mesenteric lymph nodes. The patient was diagnosed with DLBCL (non Hodgkin's lymphoma) stage IV IPI 4 of the thyroid with hypothyroidism. Treatment with R-CHOP21 (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy was started. After the first course of chemotherapy thyroid enlargement regressed, after the third course of chemotherapy anti-TPO antibodies decreased to 85kU/l, anti-Tg decreased to 55 kU/l, the thyroid function remained stable and in the thyroid ultrasound only the signs of thyroiditis is observed.
Conclusions
This case proves that TL, although rare, should always be considered in the differential diagnosis of patients with fast thyroid enlargement, nodules, goiter and carcinomas, because its prognosis and treatment differ substantially from the other disorders.

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P1148

Prediabetes and type 2 diabetes mellitus and risk of thyroid cancer

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Background
Increasing incidence of thyroid cancer may be attributable to sensitive diagnostic tools as well as changes in exposure to certain environmental factors. Type 2 diabetes mellitus (DM) reaches high prevalence worldwide. DM is a risk factor for many chronic disorders including cardiovascular disease and cancer. Insulin resistance (IR) is a fundamental aspect of the etiology of DM and compensatory

hyperinsulinemia could promote cancer growth. The association between DM and thyroid cancer is inconclusive.
Methods
Case–control prospective study in 698 randomly selected patients without history/treatment of thyroid disease in iodine sufficient area. The patients were screened for DM, underwent thyroid ultrasound and laboratory tests. The patients were assigned to group of prediabetes (PDM) ($n=53$; 7.6%), DM ($n=64$; 9%) and non-DM (NDM) ($n=581$). FNA (fine needle aspiration biopsy) was carried out in 224 patients.
Results
Thyroid size (ml) in DM 15.1 (9.59–21.57), PDM 13.35 (8.94–17.88), NDM 10.87 (7.94–16.2); ($P=0.001$; after adjustment for age $P=0.062$). TSH (mUI/l) in DM 2.4 (1–6.7), PDM 1.2 (0.7–2.45) and NDM 1.6 (0.85–3.6) ($P=0.65$). PDM/DM were in 40% of patients diagnosed by our screening. FNA Bethesda I ($n=22$; 9.8%), II ($n=169$; 75.5%), III ($n=13$; 5.8%), IV ($n=7$; 3.1%), V ($n=8$; 3.6%), VI ($n=5$; 2.2%). Histological examination was done in 37 patients, 19 findings were malignant (2.72%). Rate of thyroid malignancy was similar in PDM/DM 3.42% vs NDM 2.58%. In both groups the most common type of thyroid tumor was papillary carcinoma (50%; $P=0.668$). Advanced differentiated thyroid carcinoma and other histological types including poorly differentiated tumors were just in NDM group. TSH correlated negatively with thyroid size in all study groups ($r=-0.474$; $P=0$), and with thyroid nodule size just in NDM ($r=-0.357$; $P=0$). This relation remained identical after exclusion of patients with Graves-Basedow thyrotoxicosis ($r=-0.459$; $P=0$). Just in NDM and PDM groups, the thyroid size was positively correlated with HOMA IR ($r=0.303$; $P=0.001$ vs $r=0.414$; $P=0.013$), BMI ($r=0.201$; $P=0$ vs $r=0.330$; $P=0.025$) and C-peptide ($r=0.266$; $P=0.004$ vs $r=0.437$; $P=0.009$).
Conclusion
In the most insulin resistant subjects, diabetic and prediabetic group, we did not observe significantly increased risk of thyroid cancer. Thyroid cancer types with poorer prognosis were observed just in NDM. Thyroid gland is larger in DM, but ageing is essential part of this growth. TSH represents major stimulus of thyroid growth. However, other growth factors besides TSH must be involved.

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P1149

The mitochondrial DNA control region might have useful diagnostic and prognostic biomarkers for thyroid tumors

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Background
It is currently present in the literature that mitochondrial DNA (mtDNA) defects are associated with a great number of diseases including cancers**.** The role of mitochondrial DNA (mtDNA) mutations/variations in the development of thyroid cancers is a highly controversial topic. In this study, we aimed to investigate the role of mt-DNA control region (CR) variations in thyroid tumor occurrence and the influence of mtDNA haplogroups on susceptibility to thyroid tumors in Turkish population.
Material and method
For this purpose, totally 108 hot thyroid nodules (HTNs), 95 cold thyroid nodules (CTNs), 48 papillary thyroid carcinoma (PTC) samples with their surrounding tissues and 104 healthy control subject's blood samples were screened for entire mtDNA CR variations. MtDNA D-loop CR was screened by using Sanger sequencing. The obtained DNA sequences were evaluated and mitohaplogroups were determined with the mitomaster, a web-based bioinformatics tool.
Results
MtDNA haplogroup U was significantly associated with susceptibility to benign and malign thyroid entities on the other hand J haplogroup was associated with a protective role for benign thyroid nodules. Besides, 10 SNPs (T146C, G185A, C194T, C295T, D568, G16129A, C16292T, T16304C, A16343G and T16362C) in mtDNA CR were associated with the occurrence of benign and malign thyroid nodules in Turkish population. By contrast with the healthy Turkish population and HTNs, the frequency of C7 repeats in D310 polycytosine sequence was found higher in CTN and PTC samples (χ^2 test; $P=0.04$) Beside this, the frequency of somatic mutations in MSI regions including T16189C and D514 CA dinucleotide repeats were found higher in PTC samples than the benign thyroid nodules (χ^2 test; $P<0.0001$, $P=0.0003$ respectively). Conversely, the frequency of somatic mutations in D310 MSI was detected higher in HTNs than CTNs and PTCs ($P=0.04$).
Conclusion
This study reveals that U haplogrup is associated with the susceptibility to benign and malign thyroid tumor occurrence in Turkish population. Although mtDNA D310 instability does not play a role in tumorigenesis of the PTC, the results indicates that it might be used as a diagnostic clonal expansion biomarker for premalignant thyroid tumor cells. Beside this, D514 CA instability might be also used as prognostic biomarker in PTCs.

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P1150

Papillary carcinoma detected incidentally in a patient with Graves' disease

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Introduction
Graves' disease is an autoimmune thyroid disease presenting with hyperthyroidism. In Graves' disease, there may be diffuse enlargement in the thyroid gland, as well as nodular appearance. The risk of papillary carcinoma should always be kept in mind while the risk of malignancy is low in Graves' disease.
Case presentation
A 50-year-old woman was admitted to our center for a second-time exacerbation of hyperthyroidism in 2015. Her history revealed a diagnosis of Graves' disease in 2008 and her disease was in remission in the first year of treatment. She was referred to our center with the reason that the remission cannot be achieved after starting propylthiouracil treatment. In admission the ultrasound findings are,the right thyroid lobe was $19\times14\times45$ mm, left lobe was $24\times19\times53$ mm, and isthmus was 2.2 mm. It also showed heterogeneous parenchyma echogenicity for both thyroid lobes, due to the millimetric hypoechoic areas compatible with thyroiditis while there was no nodular appearance. Thyroid stimulated receptor antibody levels were 2.54 U/l(0–1.5). Ophthalmologic examination did not suggest thyroid ophthalmopathy. We stopped propylthiouracil treatment and started methimazole. In the follow-up of the first year euthyroid state was achieved with methimazole treatment, however hyperthyroidism emerged when methimazole dose reduced. In this period, increased levels of thyroid stimulated receptor antibody were detected (4.2 U/l). Euthyroid state could not be established despite the maximal dose of methimazole. Thyroid stimulated receptor antibody levels were 12 U/l. Surgery was planned after establishing euthyroid state with plasmapheresis therapy. Total thyroidectomy was performed and pathology revealed papillary microcarcinoma with follicular variant in a 0.5 cm lesion in the left lobe under the capsule without invasion of vascular system or the capsule. The patient is followed with thyroid suppression therapy.
Discussion
It is important to follow patients with Graves Hyperthyroidism with physical examination and ultrasound in order to assess nodules. Our patient was operated because of uncontrolled hyperthyroidism, not for malignancy. Sporadic cases of thyroid carcinoma can be seen in patients with Graves Hyperthyroidism.

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P1151

Determination of the BRAF V600E mutation prevalance at papillary thyroid carcinomas (PTCs) in Turkish population

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Introduction
BRAF V600E substitution is one of the most common mutation in PTC in different populations, and is associated with poor prognosis of the classical

variant of PTC (CVPTC) such as extrathyroidal expansion, vascular invasion, lymph node metastasis and recurrence of the disease. The purpose of this study is to determine the prevalence of BRAF V600E mutation in subcell- types of the PTCs in Turkish population.
Materials and methods
A total of 191 patients diagnosed with PTC admitted to Dr. Lutfi Kirdar Kartal Education and Research Hospital, Istanbul, were retrospectively analyzed. Clinical and pathologic factors including age, gender, PTC subtype, thyroid capsule invasion, extrathyroidal tissue invasion, and lymph node metastasis were obtained from patients' medical records. DNA was extracted from FFPE tissue samples. The BRAF gene region including V600E mutation was screened by using high resolution melting curve analysis (HRMA) and the precise localisation of mutations were confirmed by using DNA sequencing with Sanger method.
Results
One hundred and nine patients were diagnosed as CVPTC, 37 were macrocarcinoma and 72 were microcarcinoma. Sixty-five were diagnosed as Follicular variant of PTC (FVPTC), seventeen were diagnosed as Oncocytic variant of PTC (OVPTC). A mutation at 15th exon of the BRAF gene was detected in 23 of the 37 macroCVPTC patients. Nineteen out of twenty- three of these mutations were BRAF V600E, 1/23 was BRAF V600V and 3/23 were BRAF F583Y. Seventeen of the 72 microCVPTC cases were harbored with one of the BRAF mutations. Fifteen of them were BRAF V600E (20.8%) and only two of them were V600V mutation. Two mutations were detected in 37 macroFVPTC patients, one being BRAF V600V, while the other was BRAF V600E mutation (2.7%). Besides, two of the 28 microFVPTC cases (7.1%) were harbored with BRAFV600E mutation. Four of 12 macroOVPTC cases had one of the BRAF mutation. One of them was BRAFF595L and the others were BRAFV600E (25%). One of the microOVPTC case had BRAFV600V mutation. When mutation positive tumor samples were compared with mutation negative ones in classical variant group(CVPTC), thyroid capsule invasion, extrathyroidal tissue invasion, and lymph node metastasis were associated with BRAF mutations independent from tumor size ($P < 0.05$ for each).
Conclusion
Considering that BRAF V600E mutation is correlated with poor prognosis of the disease according to the obtained data, larger population based studies are necessary in order to follow up the prognosis of the PTC patients in Turkish population.

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P1152

Association between Ospital ng Makati-based thyroid ultrasonography descriptive findings and fine-needle aspiration biopsy with histopathology in the diagnosis of thyroid malignancies

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Statement of the problem
Thyroid nodules are one of the most common clinical problems encountered today. Detection of these nodules have been augmented with ultrasonography and fine needle aspiration biopsy (FNAB). Worldwide, the use of international standards of reporting such as the American Thyroid Association (ATA) Sonographic Pattern Risk Assessment and the Bethesda System for Reporting Thyroid Cytopathology have been proven to detect thyroid malignancies. However, ultrasonographic descriptions and FNAB reports are different at the Ospital ng Makati (OSMAK), wherein these are described in ways that deviate from international standards. Thus, the study aimed to validate the association of these OSMAK-based reports with the histopathology results, and to determine their accuracy in detecting malignancy as confirmed by histopathology.
Methodology
A retrospective cohort study was utilized among patients 20 years old and above with thyroid malignancies who had thyroid ultrasonography and FNAB done at OSMAK between January 2012 and January 2017. Descriptive statistics were utilized to present the variables. Review of thyroid ultrasound descriptions and FNAB were done based on common descriptive findings seen on reports. The association between these findings and the histopathologic findings were done through Fisher's Exact Test. The accuracy of these OSMAK-based descriptions and reports were then analyzed.
Findings
It was determined that there was not enough evidence to conclude that OSMAK-based thyroid ultrasonography was associated with histopathologic findings ($P = 0.135$) and the test had an accuracy of detecting malignancy at 40.5%. Also, there was also not enough evidence to conclude that OSMAK-based FNAB was associated with histopathologic findings ($P = 0.083$), and the test had an accuracy of 56.8%.
Conclusion & Significance
The use of OSMAK-based ultrasonography and FNAB reporting are not accurate in detecting thyroid malignancies. Hence, the use of validated, internationally-accepted guidelines should be implemented to help physicians provide the most appropriate care for these patients.

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P1153

Thyroid gland metastasis from a laryngeal mucinous adenocarcinoma: a case report

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Introduction
Despite its high vascularity, metastases to the thyroid is rare. The frequency of metastasis in routine practice is less than 0.2% of thyroid malignancies.
Clinical case
An ambulatory 48-year-old male presented with a two-month history of enlarging anterior neck mass that moves with deglutition, slowly growing in size, associated with hoarseness later in the course of the disease. He had no pertinent past medical history. Fine needle aspiration biopsy report: papillary thyroid cancer. CT scan was done and revealed a $5 \times 3 \times 5$ cm mass occupying almost the entire thyroid gland, but protruding to the lumen of the trachea and obliterating the upper portion of esophagus. The patient underwent total thyroidectomy, laryngectomy with tracheostomy. Pathological examination revealed the presence of abundant mucus secreting agglomeration of large atypical cells. Findings were consistent with mucinous adenocarcinoma involving the right thyroid lobe, isthmus and larynx. There was noted lymph node metastasis involving 15 out of 19 level II to V neck lymph nodes. Immunohistochemistry showed that the tumor stained negative for thyroid transcription factor-1 and thyroglobulin. This is consistent with a metastatic tumor rather than a primary thyroid cancer. CK 7 was positive, CK 20 was negative, consistent with a pulmonary origin of the tumor. A PET scan was done a month after surgery, which showed extensive metastatic disease. There was noted FDG positivity of bilateral noncalcified pulmonary nodules, cervical lymph nodes at all levels, esophagus, liver, gastric wall and mesenteric soft tissue masses and nodules. Due to the widespread metastases he opted to be treated with palliative radiotherapy. Two months later, the patient died.
Conclusion
Metastasis to the thyroid is rare but may indicate extensive disease. In patients presenting with an anterior neck mass, an FNAB may not be sufficient to clinch the diagnosis and staining for specific cancer markers may be necessary.
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P1154

Circulating thyroid autoantibodies are more sensitive than fine needle aspiration in detecting metastatic thyroid cancer

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Introduction
Follow up of differentiated thyroid cancer requires periodic measurements of thyroglobulin (Tg) and Tg autoantibodies (TgAb) and neck ultrasound. Recurrence is suspected in presence of rising levels of Tg and/or TgAb. Positive cytology or detectable Tg in washout of fine needle aspiration (FNA) of neck lymph nodes or 131-I neck uptake confirm the diagnosis of metastatic lymph node.
Case report
We report on a 25 year-old Caucasian man, affected by a classic variant papillary thyroid carcinoma with lymph nodal involvement and lymphocytic thyroiditis who underwent total thyroidectomy plus central compartment lymph node dissection. Three months later he underwent residual thyroid tissue ablation by 131-I activity (30 mCi). A neck ultrasound performed 6 months later showed two lymph nodes suspicious for metastatic disease. In the following four years lymph

nodes did not enlarge. Both cytological examination and measurement of Tg in washout turned out negative in two occasions. Tg remained undetectable while TgAb rose from a pre-surgical level of 16 IU/mL to 259 IU/mL. We treated the patient with a second 131-I activity (140 mCi). Whole body scan turned out negative. Because of this we decided to perform FNA of the suspicious lymph node which in the meanwhile was slightly enlarged (16 mm). Cytological examination was diagnostic for metastatic disease and Tg in washout fluid was 123 ng/mL. The patient subsequently underwent lymphoadenectomy. The histological examination confirmed the diagnosis of metastatic lymph node.
Conclusion
In this patient the rising of serum TgAb was the most sensitive marker predicting the recurrence of differentiated thyroid cancer. Indeed TgAb rise, in spite of constantly undetectable serum Tg and repeatedly negative FNA of neck lymph nodes, suggested the correct treatment.

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P1155

Are there any differences between hot and cold nodules according to cytology and histopathology results?

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Introduction
Many recent studies have shown that detection of an incidental thyroid cancer among patients operated for a toxic thyroid disease is not infrequent. We aimed to compare cytology and histopathology results of cold, warm and hot nodules in patients who had thyroidectomy due to toxic multinodular goiter (TMNG).
Methods
The cytology, histopathology and scintigraphy records of 1069 thyroid nodules from 413 patients who had operation with TMNG were reviewed in this study. The nodules were categorized as hypoactive (cold), normoactive (warm) and hyperactive (hot) groups according to scintigraphy. 0f 1069 nodules, 560 with undetermined scintigraphic activity were excluded. The cytology and histopathology results were compared.
Results
Of these 413 patients (118 men, 295 women), 23 (5.6%) had malignant and 390 (94.4%) had benign histopathology. In malignant group, 16 patients had papillary thyroid carcinoma (PTC), 3 had follicular thyroid carcinoma (FTC), 1 had an undifferentiated thyroid cancer (UTC), and 3 had thyroid tumors of uncertain malignant potential (TT-UMP). The 509 thyroid nodules were grouped as normoactive [$n=23$ (4.5%)], hypoactive [$n=122$ (24.0%)], and hyperactive [$n=364$ (71.5%)] according to scintigraphy. Cytological evaluations of 23 normoactive nodules were as follows: 7(30.4%) nondiagnostic (ND), 15(65.2%) benign, 1(4.3%) suspicious for follicular neoplasia (SFN). The cytology of 122 hypoactive nodules were ND in 25(20.5%), benign in 86(70.5%), atypia of undetermined significance (AUS) in 5(4.1%), follicular lesion of undetermined significance (FLUS) in 3 (2.5%), SFN in 1(0.8%), and finally suspicious for malignancy (SM) in 2 (1.6%). The 364 hyperactive nodules were determined as ND, benign, AUS, FLUS, SFN, SM, and malignant in 80 (22%), 259(71.2%), 10(2.7%), 7(1.9%), 2 (0.5%), 2 (0.5%) and 4 (1.1%), respectively. There were no differences according to cytological results between groups ($P=0.616$). Histopathology of normoactive nodules were PTC in 1(4.3%) nodule and benign in 22 (95.7%) nodules. However, 7 (5.7%) nodules had PTC and 1 (0.8%) nodule had FTC, 114 (93.4%) nodules had benign histopathology in hypoactive group. Histopathologies of the hyperactive group were as follows; 8 (2.2%) nodules with PTC, 2(0.6%) with FTC, 1(0.3%) with UTC, 3 (0.8%) with TT-UMP, and 350 (96.1%) nodules with benign pathology. There were no differences according to histopathological results between groups ($P=0.905$).
Conclusion
Recently, incidental papillary carcinomas originating from hot nodules have been reported. Contrary to conventional knowledge, we demonstrated similar malignancy rates in hot nodules when compared with cold and warm nodules.

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P1156

Diagnostic accuracy of CNB in tyroid nodules smaller than 1 centimeter

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Current guidelines suggest sonographic follow-up in thyroid nodules smaller than 10 mm with intermediate or highly suspicious features as ultrasound-guided FNAC has poor results in these nodules, and the risk of non-diagnosed thyroid carcinoma is very low. CNB has proved superior to repeated FNAC in case of insufficient or indeterminate first FNAC.
Objective
Evaluate diagnostic accuracy of CNB in nodules smaller than 10 mm with intermediate or high suspicious ultrasound (US) features.
Methods
Retrospective evaluation of all nodules CNB performed to thyroid nodules smaller than 1 cm in a tertiary center between 2006 and 2015. Evaluation included demographic data, US features, histological result, and surgical result when operated.
Results
CNB on 245 nodules, all with suspicious features on US, were included: size 3–9 mm (41 of them ≤ 5 mm); 230 solid; 88.6% in women; 166 (67.8%) in multinodular goiters, 89 of them with simultaneous CNB in a different nodule. Histological study showed: 11 insufficient samples (4.5%); 176 benign (71.8%, 26 inflammatory); 12 follicular proliferation (4.9%, 3 of them oxyphilic), and 46 malignant (18.8%, one medullary thyroid cancer and 45 papillary thyroid cancer, PTC). All non-operated nodules with insufficient or benign CNB and three with follicular proliferation were controlled 2–10 years after first CNB, 7 of them with a second benign CNB, and there was not US changes in this period. On surgery, all cases of malignant diagnosis were confirmed, 1 PTC was diagnosed among 9 resected nodules with diagnosis of follicular proliferation on CNB and 2 PTC were diagnosed among 19 resected nodules with benign CNB. The false negatives were one case of painful Hashimoto's disease that required surgery in which CNB missed the target, and a case that was operated by other nodule with follicular proliferation in the same gland in which the CNB showed subtle atypia but was not enough to diagnose malignancy. Sensitivity to detect malignancy was 95.9% and positive predictive value 79.7%. Specificity was 94% and negative predictive value was 98.9%. C- CNB may be a useful and feasible technique to study suspicious thyroid nodules smaller than 10 mm. This technique shows high sensitivity and PPV to detect malignancy and very high specificity and NPV, making follow-up unnecessary in most of cases.

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P1157

Serum thyroglobulin (sTg) before surgery in euthyroid patients with differentiated thyroid cancer (DTC)

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sTg is universally accepted as the best marker of disease status in DTC. Its presurgical serum level may suggest the presence of distant metastasis in case of very high level, but the correlation between its level and the characteristics of the tumour is yet to be defined.
Objective
To evaluate preoperative thyroglobulin as predictor of DCT features.
Methods
Preoperative sTg was measured in patients operated for DTC between 2011–2017. Patients with positive anti-Tg Ab, treated hypothyroidism, not controlled hyperthyroidism or controlled autoinmune hyperthyroidism were excluded. We evaluated the influence of extrathyroidal extension (ETE), positive lymph node (LN), cytological variant (CV), BRAF mutation, ATA 2015 risk and multifocality on sTg levels. sTg divided (adjusted) by thyroid weight (sTg/weight in grams) after thyroidectomy was also considered in order to reduce the effect of Tg secretion by non-neoplastic tissue, as well as its value corrected by TSH concentration and tumour size (main focus or global size).
Results
130 CDT (4 FTC, 126 PTC) were included. Median presurgical sTg was significantly lower in DTC with ETE (59.2 vs 106 ng/ml; $P<0.04$), and the

difference persisted when corrected by preoperative TSH (27.1 vs 50.5), glandular weight (2.3 vs 4.5), both parameters (1.2 vs 2.6) as when divided by bigger size (sTg/BS) (5.3 vs 8.5) or global size (sTg/GS) of DTC (2.3 vs 3.5). The differences persisted when preoperative TSH adjusted sTg/BS and sTg/GS. Total and corrected sTg also showed significant differences when DCT were grouped by LN (lower when positive), CV (lesser in classical in opposite to follicular variant), BRAF V600E (lower if present) and ATA2015 risk (lower in intermediate risk versus low risk). Multifocal neoplasm showed no difference in sTg levels when compared with DCT with a single lesion. There were 8 high risk DTC (ATA2015): 2 FTC (one with pulmonar metastasis and other with extensive vascular invasion), and 6 PTC:, one metastatic, 4 with lymph nodes larger than 30 mm and one with gross extrathyroidal invasion, all diagnosed before surgery. These patients collected the highest level of sTg. C - DTC aggressiveness defined by ETE, BRAF V600E positive, pN1 and ATA risk, associates less efficient thyroglobulin secretion, both gross value and TSH corrected levels. This parameter may be a helpful tool for surgical planning, demanding a thorough approach in DCT with low levels of sTg.

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P1158

Coexistence of papillary thyroid carcinoma and autoimmune thyroid disease

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Introduction
Papillary thyroid carcinomas (PTC) represent up to 87% of all thyroid cancers with an incidence that has doubled over the past 30 years. Hashimoto's thyroiditis (HT) and Graves' disease are two autoimmune thyroid diseases representing the most common causes of hypothyroidism and hyperthyroidism, respectively. Although PTC with coexisting HT has been reported in literature, its association with GD is not a common condition. Herein, we report three cases of coexisting papillary thyroid carcinoma and autoimmune thyroid disease: HT in one case and GD in two cases.
Observations
The first case reported a 30-year-old-woman, who has been followed during three years for HT. Her thyroid ultrasound examination revealed a multinodular goiter with a suspicious nodule. Fine needle aspiration cytology showed features of PTC. Total thyroidectomy with lymph node dissection was performed to the patient and postoperative histopathological examination showed the PTC. The second case was a 69-year-old woman who was initially followed for GD with Graves'ophtalmopathy. Her thyroid ultrasound examination showed heterogeneous hypoechoic nodule in the right lobe. After medical preparation, the patient had a total thyroidectomy and the histopathological examination revealed a follicular variant of PTC. The third case reported a 34-year-old man, who presented with symptoms of thyrotoxicosis. On physical examination, he had an asymmetrical goiter with a right nodule measuring 2 cm $\times$ 1 cm. Thyroid scintigraphy image was consistent with the diagnosis of GD. Fine needle aspiration biopsy of the right nodule revealed features of PTC. After medical preparation, a total thyroidectomy with lymph node dissection was performed. Histopathological examination confirmed PTC.
Discussion
The pathogenic linkage between autoimmune thyroid diseases and PTC remains unclear. In the case of GD, studies have suggested that thyrotropin receptor antibodies may possibly play a role in the initiation and progression of thyroid cancer. Conversely, many hypotheses have been suggested to explain the relationship between HT and PTC, one of which is the concept of chronic inflammation leading to a neoplastic condition. In patients with autoimmune thyroid disease, thyroid ultrasound should be performed in order to detect suspicious thyroid nodules warranting cytologic analysis.

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P1159

Analysis of the prognostic factors during I-131 therapy for differentiated thyroid cancer patients using BIOMAT ENDO data base

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BIOMAT-ENDO software is a *Windows Forms* application that stores all the main data regarding the patients with thyroid cancer (TC) hospitalized in the *Nuclear Medicine Department* of the National Institute of Endocrinology *in Bucharest,* starting with the first hospitalization, continuing with the periods of radioiodine therapy (RIT) and the follow up. Patient-monitoring MODULE contains clinical parameters, surgery details, in Vivo and in Vitro investigations, therapy information. Correlations can be done between any input data. Until now 2000 cases hospitalized during the last 50 years were digitalized in this data base.
Materials and methods
We selected 300 patients who had undergone a total thyroidectomy and subsequent I-131 therapy. Including criteria: at least two I-131 therapies, whole body scan result (WBS), serum TGL and AntiTGL values. Analysis also includes parameters associated with the curative effect: gender, age at diagnostic, risk factors (endemic/non-endemic area), environmental origin, surgical procedure, histopathologic diagnosis. We used Q15L to verify the correctness of existing data and for some statistical results.
Results
In the studied group there is a prevalence of DTC among women (84%) over 45 year, most of them from the urban area (70%). Endemic zones are the main area risk factor (70%). *Preablative* distribution of stimulated TGL values was: $<$ 2–10 ng/ml (35%), 10–100 ng/ml (39%) and $>$ 100 ng/ml (26%) with mean value $=$ 107.93 $\pm$ 278.25 ng/ml. Positive Anti TGL at the first RIT are present in 21% of patients. 96% of patients were with positive WBS. *After the RIT* (therapies number: 5.4 $\pm$ 3.6, cumulative dose: 382.6 $\pm$ 280 mCi) a significant decrease of TGL was found (mean 0.672 ng/ml, $P<$ 0.01) at 82% of the cases. WBS results were negative for 81% of patients. Not responding cases, with high TGL values and positive WBS after RIT, represented 18%.
Conclusion
Our study indicates that most DTC patients can obtain partial or complete remission after I-131 therapy. I-131 imaging and TGL levels at diagnosis are both important indicators to evaluate the curative effect. The analysis of efficacy and prognostic factors of RIT have the benefit to establish individualized treatment strategy, predict curative effect and assess the prognosis for those DTC patients. The clinical data reviewed revealed which biological features are predominant for a good overall prognosis of thyroid cancer, which patients are still with persistent/recurrent disease according to the measured serum thyroglobulin (TGL) levels and imagistic findings.

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P1160

Treatment strategies in medullary thyroid carcinoma – outcome following initial surgery with a curative, debulking or prophylactic intent

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Medullary thyroid carcinoma (MTC) is a rare malignancy which has often metastasised at time of diagnosis. Surgical resection represents the only prospect for cure. However, debulking neck surgery may be beneficial in advanced cases. Prophylactic surgery is increasingly undertaken in asymptomatic patients with known mutations in the *RET* oncogene. The aim was to describe the outcome following initial surgical treatment for MTC at our institution. We performed a retrospective analysis of medical records of patients diagnosed with MTC and followed up at our centre. Study period extended from 1976 to 2016. Data recorded included demographic, clinical, biochemical and radiological variables. Sixty five patients (27 men) were identified - 36 (55%) sporadic and 29 hereditary cases. Median age at diagnosis was 37 years. Sixty one patients underwent neck surgery, 14 (22%) received adjuvant neck radiotherapy and 4 (6%) received palliative care only. Median overall follow-up 9.3 years. Nine patients (15%) were deemed to have incurable disease but underwent debulking neck surgery – all had stage IV disease. Three patients died of MTC – median survival 23 months. Six (67%) were alive at last follow-up – two had progressive and four stable disease. Thirty six patients (59%) had neck surgery with a curative intent. Seventeen (47%) were in remission post-operatively – subsequently, two patients experienced recurrence. Nineteen patients (53%) did not achieve biochemical remission (normal basal serum calcitonin) post-operatively – disease progression was later detected in 7 patients. Three patients in the "curative intent" group died of MTC – median survival 171 months. Sixteen asymptomatic patients (26%) with germline mutations in the *RET* oncogene underwent thyroidectomy – so

called "prophylactic thyroidectomy". Median age 24 years; median follow-up 21.5 years. Post-operative biochemical remission was achieved in 10 patients (63%) – one experienced recurrence. All patients in this group were alive at last follow up except one who died of renal carcinoma. In conclusion, neck surgery may induce long-term remission in half of patients with MTC who have potentially resectable disease. However, in advanced or incurable disease, debulking surgery may be useful in selected patients.

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P1161

Thyroid cancer prevalence and pathological features in thyroidectomy patients – five years experience

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Objectives
In the last decades, thyroid cancer incidence has increased all over the world. This may be due to heightened medical surveillance and more addressability to surgery, as many cancers are diagnosed while under 1 cm. The aim of our study was to obtain data about the prevalence and histological subtypes of primary thyroid carcinoma in patients undergoing thyroidectomy.
Materials and methods
We retrospectively analysed the files of 953 patients who underwent thyroidectomy in our surgery department between January 2012- December 2017. Anthropometric, biologic and imagistic data, indication of thyroid surgery, surgical procedures and pathology results were recorded.
Results
222 (23 .29%) patients had a diagnosis of primary thyroid carcinoma. The primary indications for thyroid surgery included: 5 (2.3%) Graves' disease and nodular goiter, 181 (81.5%) multinodular goiter, 23 (10.4%) uninodular goiter and 13 (5.9%) thyroid cancer. The mean age at diagnosis was 52.49 ± 13.79, range 20-83 years, but 61 (27.47%) were diagnosed before the age of 45 years. The female to male ratio was $180{:}42 = 4.28$. The surgical procedure was lobectomy in 3 and total thyroidectomy in the remaining 219 patients. 207 (93.24%) suffered from differentiated thyroid carcinoma [194 (87.38%) papillary, 13 (5.85%) follicular], 7 (3.15%) from medullary thyroid carcinoma, 4 (1.8%) from poorly differentiated and 4 (1.8%) from anaplastic thyroid carcinoma. Multifocality was present in 62 (27.9%) patients. Pathological tumor stage was: T1 in 99 (44.6%), T2 in 38 (17.1%), T3 in 76 (34.2%) and T4 in 9 (4.1%) patients. 78 (35.1%) patients had tumors of 1 cm or less in diameter. 79 (35.6%) patients associated histopathologic chronic autoimmune thyroiditis.
Conclusions
One in five patients who underwent thyroidectomy had a thyroid cancer. This might be due to a real increased incidence of thyroid cancer or just a result of better selection of patients for surgery and diagnose of microcarcinomas that otherwise would have gone unnoticed. Papillary thyroid carcinomas constituted the vast majority of these neoplasms, this being usually associated with an iodide-sufficient area.

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P1162

A case of familial follicular thyroid carcinoma

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Introduction
Familial follicular cell-derived tumors may account 5–15% of thyroid carcinoma cases. Defined as the attainment of two or more first-degree relatives by thyroid cancer in the absence of a known familial syndrome. When three or more family members are affected, the probability that the disease has a familial origin is 99.9%. We report the case of a family of 4 siblings affected.
Observation
- Patient aged 43 years, without a personal or family history particular, had a total thyroidectomy for a left lobe nodule classified Tirads IVb of 25 mm, anatomo-pathological study: papillary micro carcinoma of 4 mm vesicular variant and constituted of 80% of oncocytic cells.
- His sister 46 years had a total thyroidectomy for a suspected nodule Tirads V, anatomo-pathological study: 4 cm nodule with a well-differentiated vesicular carcinoma with vascular invasion of the capsule.
- Another sister 40 years operated as a part of screening with anatomo-pathological study: papillary carcinoma in its vesicular variant, encapsulated and bifocal.
- A brother 33 years, had a total thyroidectomy for a Tirads VIb nodule, anatomo-pathological study: papillary carcinoma in its solid variant.

Discussion
It is now widely recognized that familial cancers are more aggressive than sporadic ones. Characterized by, tumor multifocality, local invasion with lymph node metastasis, and local or regional recurrence. At present, the specific genetic basis is not clear. Studies suggest that familial cancers has an autosomal dominant behavior with incomplete penetrance and variable expression. Early diagnosis and treatment are very important to improve the quality of life and survival of patients.

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P1163

Co-incidence of medullary and papillary thyroid carcinoma

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Introduction
Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma and is derived from thyroid follicular cells which originate from the endodermal origin. In contrast, medullary thyroid carcinoma (MTC) is rare and originates from the parafollicular C-cells, which are commonly thought to be derived from the ectodermal neural crest. Co-incidence of the two condition on the same patient is so rare. We describe a case of concurrent MTC and PTC occurring in the same thyroid lobe.
Case report
A 63-year-old woman was referred to our hospital for further evaluation of thyroid nodules. Ultrasound assessment revealed two nodules in the right lobe, 10.3 mm and 14.4 mm in size with accompanying calcifications. Her serum levels of calcium, parathormone, carcinoembryonic antigen, thyroid stimulating hormone and free thyroxine were normal. The baseline serum calcitonin level was 139 pg/ml (normal range [NR] <11.5 pg/ml). There were no antithyroid autoantibodies. A single fine-needle aspiration biopsy (FNAB) was applied, the result was suspicious for malignancy. Abdominal US was negative for adrenal nodules as well as urinary catecholamines and metanephrine levels were within normal limits. Total thyroidectomy was performed. The pathological examination revealed the presence of a tall cell type papillary carcinoma of the right lobe (1.5 cm) with an adjacent medullary microcarcinoma (0.6 cm). The tumour cells were positive for calcitonin. The postoperative TSH level was 40 mIU/ml (NR 0.3–4.9) and calcitonin level was <2 pg/ml. The patient was discharged without any complications. An ablative dose of iodine 131 treatment is planned.
Discussion
The synchronous occurrence of multiple thyroid carcinomas of different origin in the same patient is extremely rare, representing less than 1% of all thyroid malignancies. Interestingly, the incidence of PTC in patients with MTC is greater than that of PTC in patients undergoing thyroidectomy for non-malignant conditions, suggesting the presence of a common pathogenic etiologies. Even if it can be coincidental, possible hypotheses for the synchronous occurrence include involvement of the RET proto-oncogene in both PTC and MTC and an unidentified common mother cell with a capacity for differentiating parafollicular C cells and epithelial follicular cells which can be the origin of the cancer. Beacuse there is a lack of marked differences in the ultrasonografic features between MCT and PTC, the possibility of the coexistence must be taken into account. Since there is no evidence of a certain cause of this condition more data is needed from additional geographic areas and populations.

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P1164

The prevalence of concomitent non-medullary thyroid carcinoma and primary hyperparathyroidism

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Introduction
Synchronous medullary thyroid cancer and pHPT is common in MEN-2A (Sipple syndrome). In contrast, concomitant nonmedullary thyroid cancer and primary hyperparathyroidism (PHPT) is very rare even if the pathological relationship between parathyroid and thyroid diseases is common.
Aim
Was to determine the prevalence of non-medullary thyroid carcinoma in patient who underwent neck exploration for PHPT.
Patients and method
Retrospective study of 259 patients who suffered surgery interventions for hyperparathyroidism at the University Emergency Hospital "St. Spiridon", Iasi, Romania. Data regarding parathyroid affections, surgical procedures and histological results were recorded.
Results
A total of 259 (198 women and 61 men) parathyroidectomies were performed between 2010-2016 at our hospital (parathyroidectomy only for 136 cases and concomitant thyroidectomy for 123 patients). Among 192 patients with PHPT, 103 also underwent thyroidectomy. The concomitance of HPTP and non-medullary thyroid carcinoma was found in 33 cases (29 women and 4 men). The occult papillary carcinoma was present in 25 (75%) cases, papillary carcinoma in 7 (21, 2%) cases and follicular carcinoma in 1(3%) case. The final prevalence of PHPT and non- medullary carcinoma was 32%.
Conclusion
Our results are in accordance with the main caracteristics of the association between PHPT and non-medullary thyroid carcinoma: more frequent in women, most cases are classical variant of occult papillary carcinoma, bilateral thyroid involvement and lymph node metastasis are very rare. However the high prevalence rise the question if the association between thyroid non-medullary carcinoma and PHPT may be coincidental or is something more to research?

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P1165

Visualization of Hepatic Metastases of Medullary Thyroid Carcinoma on Tc-99 Bone Scintigraphy

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Medullary carcinoma of the thyroid (MCT) is a tumor developed at the expense of the thyroid parafollicular cells, and secretes the polypeptide hormone calcitonin. It is known as an aggressive tumor that metastasizes early. Case Report: We describe a case of a 57 year-old women, who presented a neck mass, for which she underwent a total thyroidectomy associated to a bilateral neck dissection and was diagnose as MCT. Post operatively calcitonin remained elevated (19000 pg/ml). Computed tomography reveled multiples calcified masses in the liver, consisting in hepatic metastases. In the other hand bone scintigraphy with technitium-99m demonstrated not only multiples metastatic lesions in lumber spine but also extensive areas of uptake of Tc99 m in the liver. Liver uptake of technetium-99m MDP in hepatic MTC metastasis has rarely been reported in previous publications. Possible mechanisms of uptake might include adsorption of amorphous calcium due to the fact that these tumors do calcify. Other possibilities include calcitonin– calcium metabolism, active sequestration, or secretion of one of the tumor hormones.

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P1166

Descriptive analysis of papillary thyroid microcarcinomas in a single-center

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Introduction
The incidence of papillary thyroid microcarcinomas (MPT, max diameter ≤ 10 mm) has increased in recent years. Most have a very good prognosis but some have growth during follow-up, lymph node and / or distant metastases.
Material and methods
We performed a single-center, retrospective cohort study, n = 114 patients (86% women, average age 48.3 years), diagnosed with MPT between 1998 and 2012. Risk stratification system (ATA 2015): 10 high, 34 intermediate and 70 low risk at the diagnosis. Therefore, 38,6% had extrathyroid disease. The prevalence of certain clinical and histological characteristics that could predict a worse evolution was studied. We also analyzed excellence response (RE), indeterminate (RIN), biochemical incomplete (BIN) and structural incomplete (EIN) in the different ATA groups after 2 and 5 years. In low risk group, we differentiated those who had not received iodine. Statistical analysis SPSSv.15.0.
Results
Univariate and descriptive analysis according to ATA groups 1, 2 and 3: age (53.2 ± 14.4, 41.7 ± 12.2, 33 ± 18 years; $P = 0.004$), male sex (4.3, 26.5, 40%; $P < 0.001$), incidental diagnosis (51.4, 17.6, 0%; $P < 0.001$), isthmus location (7.1, 14.7, 0%; $P = 0.01$), capsular invasion (4.3, 44, 40%; $P < 0.001$), vascular invasion (0,2, 4.5%; $P = 0.07$), tumor size (5.9 ± 0.4, 6.1 ± 0.3, 6.5 ± 0.3 mm; $P = 0.015$), previous TSH (1.8 ± 1.4, 2.0 ± 0.6, 2.1 ± 1.2; $P = 0.09$). Isthmus location was associated with N1 ($P = 0.005$). Initial treatment: hemithyroidectomy (8.5,0,0%), central lymphadenectomy (8.6, 26.5, 40%), lateral (1.4, 50, 80%), radioiodine (32.8, 100, 100%). Retreatment after 2 years in ATA 2/3 group: 2 relymphadenectomy, 13 new radioiodine dose, 1 ethanol injection. Retreatment between 2 and 5 years in ATA 2/3: 3 surgical reintervention, 5 another radioiodine dose. Thus, 18,4% required at least one more treatment in the follow-up.

	2 years response				5 years response			
	RE	IND	BIN	EIN	RE	IND	BIN	EIN
ATA1 (Iodine yes/no)	82.61/ 66.7%	17.4%/ 33.3%	0%/2.3%	0%/0%	86.36%/ 72.3%	13.64%/ 22.26%	0%/0.04%	0%/0%
ATA2	64.52%	12.90%	12.90%	9.67%	70.83%	8.33%	12.5%	4.16%
ATA3	33%	22%	11%	33%	28.6%	42.86%	14.29%	

Conclusions
In our cohort: younger age, male sex, capsular and vascular invasion, larger tumor size and higher TSH, were more prevalent in MPTs with higher initial risk of recurrence. Only three patients presented distant metastases, and all from the diagnosis. Tumors that did not present lymph node metastases at diagnosis did not show it in the evolution either. Extrathyroidal involvement in our series was very frequent. Nevertheless, this did not translate into an increased mortality but in the need for more treatments during the follow-up.

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P1167

TSH level and risk of malignancy in patients with thyroid nodules with Bethesda IV Cytopathology System

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Introduction
Fine needle aspiration biopsy (FNAB) is the mainstay diagnostic procedure for evaluation of thyroid nodules, but it doesn't permit to distinguish between benign and malignant follicular lesions (category IV in the Bethesda Cytopathology System). Some reports have suggested an association between increased serum levels of TSH and thyroid cancer. However, the specific relationship between TSH and malignancy has been scarcely studied in follicular thyroid nodules.

Objectives
To investigate the association between preoperative TSH levels and malignancy in patients with follicular thyroid nodules.
Methods
Retrospective study of all subjects who underwent surgical treatment for Bethesda IV thyroid nodules since the adoption of the Bethesda System for reporting thyroid cytopathology in a single centre from Spain (2012–2017), and for whom a preoperative measure of TSH was available. Cytopathologic diagnosis was established by ultrasound-guided FNAB. Clinical data and ultrasound characteristics of the nodules were recorded.
Results
A total of 125 subjects were identified (mean age 52.8 ± 14.0 years, 87.2% women). Forty-nine of them (39.2%) showed malignancy upon definitive histopathological examination (21 follicular variant of papillary carcinoma, 19 follicular thyroid carcinoma, 8 other types of papillary carcinoma and 1 medullary carcinoma). Subjects with thyroid cancer were older than those with benign conditions (57.0 ± 13.7 vs 50.1 ± 13.7 years; $P = 0.007$). The presence of ultrasonographic traits of malignancy (hypoechogenicity, irregular margins, microcalcifications, taller than wide shape and central vascularization), the maximum diameter of the nodule and its calculated volume didn't differ among malignant and benign lesions. Median (range) levels of TSH were 2.35 mU/l (0.34–37.0) among subjects with thyroid cancer and 2.04 mU/l (0.09–10.94) among those with benign diseases ($P = 0.35$). The ROC analysis showed a TSH cut off point of 2.14 mU/l to differentiate benign from malignant disease (sensitivity 65.3%, specificity 56.6%, positive predictive value 50.8%, negative predictive value 71.7% and area under the curve 0.55). The proportion of subjects with TSH ≥ 2.14 mU/l was greater among subjects with cancer ($P = 0.018$). A logistic regression model including age and TSH ≥ 2.14 mU/l as independent variables showed that both of them retained independent association with malignancy (OR [95% CI] for TSH ≥ 2.14 mU/l: 2.53 [1.17–5.44]; $P = 0.018$).
Conclusions
The present study supports an association between serum concentrations of TSH and risk of malignancy among subjects with Bethesda IV thyroid nodules. In this particular group of patients TSH levels could provide greater diagnostic yield than ultrasonographic examination.

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P1168

A review of prevalence, reporting, and criteria for further investigation of incidental thyroid nodules reported on computed tomography scanning in an Irish general hospital

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The purpose of this study was to identify the prevalence of Incidental Thyroid Nodules (ITN's) on Computed Tomography (CT) scans of the chest, assess variation in reporting by radiologists and to apply recent guidance to assess which nodules may require further investigation. We performed a retrospective review of 742 CT scans which included the chest performed in a regional hospital. Thyroid abnormalities were reported in 9.8% ($n = 76$) of CT scans. There was considerable variation in reporting of nodules with the size of the nodule reported in 45% of scans with nodules present ($n = 14/31$), with five of these meeting American College of Radiology Criteria for further investigation. In the remaining 17 patients where a nodule was identified its size and shape were not further clarified. General descriptions such as 'Multiple nodules', 'Multinodular Goitre' and 'Bilateral nodularity' were given in 43% of scans with thyroid abnormality ($n = 33/76$). In these instances no discrete size of the largest nodule was given. Calcifications were reported in 10 cases. Our study highlights the heterogeneity of reporting of ITN's and the need for consistent reporting criteria in keeping with available evidence to identify nodules which may require further evaluation. Clarification and standardisation in this area can have the dual effect of reducing the need for unnecessary investigations and highlighting nodules in need of further workup.

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P1169

A review of histology reports of 675 thyroid cancer cases in a single centre over ten years

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The recently (2015) revised American Thyroid Association guidelines for the management of differentiated thyroid cancer recognise the importance of histological subtype in risk stratification. The prevalence of thyroid cancer subtypes in an Irish population is unknown. We reviewed all histology reports of thyroid carcinoma from a quaternary referral centre over a 10 year period, 2005 to 2015. 675 reports were reviewed. Of these, 87% were reported as papillary thyroid cancer (PTC), 7% follicular, 2.5% medullary, 2.5% anaplastic, 1% mixed. Absolute case numbers of thyroid carcinoma reports increased from 32 in 2005 to 111 in 2014. We then examined the annual incidence of each histological subtype (follicular variant, papillary, mixed, tall cell, insular and diffuse sclerosing) of PTC. Follicular variant PTC increased from 7/23 (30%) in 2006 to 36/90 (40%) in 2014, while other variants remained unchanged. The histological subtypes associated with higher risk, tall cell, insular and diffuse sclerosing variants all remained uncommon ($< 5\%$). The apparent increase in follicular variant PTC might reflect a change in reporting methods but also raises the possibility of a changing disease pattern over time. Re-analysis of the original histology specimens is required to answer this question. This data examination is the first review of characteristics of thyroid cancer in an Irish population. It can be used in informing future planning of services and ensure that treatment outcomes are as good as internationally predicted outcomes based on initial risk stratification.

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P1170

Evolution of tumor markers after external beam radiotherapy in the non-undifferentiated thyroid cancer

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Introduction
The role of external beam radiotherapy (EBRT) as primary or as adjuvant therapy in the non-undifferentiated thyroid cancer (NUTC) is controversial. Most published data refer to retrospective case series. Therefore, little is known about the correlation between tumor markers and radiologic measurements of tumor response.
Objectives
The study aimed to analyze the kinetics of tumor markers and radiologic measurement of tumor response after EBRT in NUTC.
Material and methods
A retrospective analysis of a series of 11 patients diagnosed of NUTC, and consecutively treated with EBRT in the Clínica Universidad de Navarra (CUN) between 2010 and 2016 was performed.
Results
Clinical characteristics: gender: women (7) and men (4); age at diagnosis: 66 years (49–68); histological subtype: follicular (7), papillary (3), and medullary (1). EBRT techniques: intensity modulation radiotherapy (IMRT) (7), three-dimensional conformal radiotherapy (3D-RTC) (3) and radiosurgery (1). The median dose of EBRT was between 21 Gy and 76 Gy, and 18 Gy for radiosurgery. Localization of EBRT: bone (7), cervical (2), cervical-mediastinal (1) and cerebral (1) region. The most frequent adverse effects were dysphagia (three patients) and dermatitis (two patients). The toxicity grade according to the criteria of the Radiation Therapy Oncology Group (RTOG) was: 1–2 (4 patients) and 3 (1 patient). The twelve-month radiological response related to the area of EBRT administration, but not with other concomitant metastasis was: stability in 5 (3 follicular, 2 papillary), regression in 2 (both follicular), and progression in 4 patients (2 follicular, 1 papillary, and 1 medullary). In the 4 patients with follicular cancer showing stability or regression, a parallel reduction in thyroglobulin levels was observed at 6 and 12 months. In the patient with medullary cancer, we observed correlation between the radiological progression and calcitonin increase at 5 years.
Conclusions
In our series, we observed a correlation between the response to EBRT regarding the tumor burden and the corresponding thyroid marker: decreasing thyroglobulin levels in follicular thyroid cancers showing stability and regression, and increasing calcitonin levels in the medullary cancer showing progression.

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P1171

Natural course of thyroid cancer nodules compared with benign thyroid nodules

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Purpose
The primary aim of this study was to evaluate changes in the diameter and volume of thyroid cancer nodules identified using fine-needle aspiration biopsy (FNAB) or surgery, and to compare the changes in size between thyroid cancer nodules and benign nodules. The secondary aim was to analyze the risk factors associated with thyroid cancer nodule growth.
Methods
A total of 96 patients with 102 nodules were enrolled in the cancer group, and 98 patients with 101 nodules were included in the benign group. All patients underwent thyroid ultrasonography at least twice at $\geq$1-year intervals.
Results
The initial mean age, gender, thyroid-stimulating hormone (TSH) levels, thyroid autoantibody levels, number of FNABs, initial maximum diameter, and initial volume did not differ between the two groups. The mean follow up durations in the cancer group and benign group were 29.5 ± 18.8 and 31.9 ± 15.8 months ($P = 0.32$), respectively. The maximum diameter change in nodule length per year was 0.40 ± 1.00 mm in the cancer group and -0.07 ± 0.77 mm in the benign group ($P = < 0.01$). The volume change (in mL and percent) per year was increased significantly in the cancer group compared with the benign group (0.06 ± 0.14 ml vs. 0.003 ± 0.05 ml, respectively, $P < 0.01$; $26.9 \pm 57.9\%$ vs. $1.72 \pm 26.0\%$ $P = < 0.01$). The initial maximum diameter and initial volume were independent risk factors for thyroid cancer nodule growth in multiple regression analysis.
Conclusion
In conclusion, the present study suggested that thyroid cancer nodules progress rapidly compared with benign nodules, as exhibited by the $\sim$30% volume increase per year. Initial nodule size was an independent risk factor for cancer nodule growth.

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P1172

Risk of thyroid malignancy in large thyroid nodules greater than 4 cm

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Background
The risk of thyroid cancer in large thyroid nodules greater than 4 cm has been reported to be increased. Some authors insist that diagnostic lobectomy should be performed in patients with large thyroid nodules, irrespective of fine needle aspiration cytology (FNA) results. However, consensus on that matter has not been met. We wanted to investigate the risk of thyroid malignancy according to the size of the thyroid nodules, based on FNA results.
Methods
FNA results of 836 patients with thyroid nodules larger than 2 cm who visited Chonnam National University Hwasun Hospital from April 2004 to March 2009 were evaluated according to size category. The nodules were categorized to three groups by maximal diameter of the nodule on ultrasonography (Group A: 2–2.9 cm, Group B: 3–3.9 cm, Group C: $\geq$4 cm).
Results
Number of patients in group A, B and C were 476, 206 and 154 and the mean sizes of the nodules in each group were 2.4 ± 0.3 cm, 3.4 ± 0.3 cm, and 4.9 ± 1.0 cm, respectively. Based on ATA ultrasonographic category, high suspicion nodules were 51(10.7%), 13 (6.3%), and 9 (5.8%, $P = 0.073$). After FNA, the Bethesda system 6 category were reported in 32 (6.7%), 14 (6.8%) and 8 (5.2%), in each group and there was no increased risk of malignancy in larger thyroid nodules ($P = 0.887$).
Conclusions
Large thyroid nodules ($\geq$4 cm) are not at higher risk for malignancy. Surgical decision should be guided by FNA result of the nodule, not by the size the nodule.

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P1173

Relationship between microRNA expression levels and tumor size in patients with papillary thyroid carcinoma

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Introduction
Despite low mortality rates of patients with papillary thyroid carcinoma (PTC), disease progression in PTC occurs in up to 20% of patients. Currently, recurrence risk stratification is accomplished by using clinicopathologic factors, despite their limited prognostic value. Some data suggest that patient age at disease onset and primary tumor size may predict the risk of disease progression. Identification of possible associations of traditional clinicopathological parameters of disease recurrence with molecular biomarkers of PTC may help better understanding the carcinogenesis and improving the clinical management of patients with PTC
Objectives
The aim of this study was to evaluate miRNA expression profiles in different age groups of patients with PTC and to compare the expression levels of miRNA in differently sized PTC tumors.
Methods
We selected 3 miRNA (miRNA-146b, -222 and -21) and measured the expression levels of these miRNAs in three patients groups according to age at disease onset (60 years and older, 40–60 years, and less than 40 years) and in patients with different PTC tumor size (2 cm or less and greater than 2 cm).
Results
The levels of miRNA (miRNR-146b, miRNR-222, miRNR-21) expression significantly differed between PTC patients with tumor size 2 cm or less ($n = 99$) and greater than 2 cm ($n = 84$). Higher expression levels of miRNAs (miRNR-146b $P < 0.001$; miRNR-222 $P < 0.001$; miRNR-21 $P < 0.001$) were observed in patients with tumor size greater than 2 cm. The expression levels of all three miRNA did not significantly differ in patients of different age groups ($P > 0{,}05$).
Conclusion
The levels of miRNA-146b, -222 and -21 expression in PTC were strongly associated with tumour size. Such difference in the expression levels could be due to the fact that in larger thyroid tumors there is a higher percentage of altered tumor cells in which the miRNA expression is severely disturbed. Selected miRNAs did not show age-related differences in expression, suggesting that mechanisms other than age may influence the expression of these miRNA.

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P1174

Correlation of preablative thyroglobulin to the new response to therapy system in differentiated thyroid cancer

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Introduction
Evidence supports the prognostic value of preablative stimulated thyroglobulin (ps-Tg) for recurrent and persistent disease in patients with differentiated thyroid cancer (DTC). The correlation of ps-Tg with therapeutic response however has been less studied.
Objective
To study the correlation of ps-Tg and the trend of serial preablative thyroglobulin measurements(DTg) with the response to treatment restaging system proposed in 2015 American Thyroid Association guidelines.
Methods
We conducted a retrospective study on patients with DTC who underwent total thyroidectomy and radioactive iodine (RAI) ablation in a tertiary referral hospital in 2009 and 2010. Patients with missing data or positive anti-Tg Abs were excluded from the study and the rest were divided in three groups in terms of ps-Tg levels: group 1, ps-Tg < 1 ng/ml ($n = 48$), group 2, $1 \geq$ ps-Tg ≤ 10 ng/ml ($n = 48$), group 3, ps-Tg > 10 ng/ml ($n = 19$). Responses to therapy were divided

in excellent (ER), biochemical incomplete (BIR), indeterminate (IR) and structural incomplete response (SIR) according to the new response to treatment system.
Results
115 patients were followed for a median of 60 months. SIR was detected in 3.4% in group 1, 8% in group 2, 20% in group 3. However, results were not statistically significant in the studied series ($\chi^2=3.435$, $P=0.179$).
Conclusion
Preablative thyroglobulin may be correlated to therapeutic response.

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P1175

May hemocytometer parameters be a biomarker in medullary thyroid carcinomas?

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Aims
Medullary thyroid carcinoma (MTC) is a rare endocrine cancer that accounts for approximately 5% of all thyroid cancers. Both the diagnosis and management of MTC could be difficult. Surgery is a main therapy in MTC, chemotherapy and external radiotherapy have limited efficacy. Recently, the relationship between some of the hemocytometer parameters and cancer has been investigated. In this study we aimed to determine the relationship between MTC and hemocytometer parameters and also evaluate whether they would be useful parameters for MTC prognosis.
Methods
Thirty six MTC who underwent total thyroidectomy in our center between 2000–2017 were included to the study. Patients' data such as neutrophil/lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), red blood cell distribution width (RDW), platelet distribution width (PDW) collected from their electronic files. Also, recurrence and metastasis ratio of MCT were evaluated by using patients' data.
Results
Twenty (55.5%) female and 16 (44.5%) male patients were included in the study. The mean age was 53.38 ± 12.87 years. The mean follow-up period was 80.30 ± 76.12 months. In the follow-up of the patients, 13 (36.1%) patients developed recurrence and/or metastasis. NLR, PLR, RDW and PDW were 3.34 ± 3.57, 163.16 ± 78.94, 15.88 ± 2.12 and 15.38 ± 7.05, respectively in patients with recurrent and / or metastasis. NLR, PLR, RDW and MPV levels were 4.51 ± 5.66, 128.97 ± 77.33, 15.23 ± 1.59 and 16.76 ± 2.36, respectively in patients without recurrence and/or metastasis. When recurrent and/or metastatic patients were compared with non-developed ones in terms of hemocytometer parameters, there was no statistically significant difference between NLR, PLR, RDW and PDW between recurrent and/or metastases positive patients and negative ones ($P>0.05$).
Conclusion
It is known that inflammation is critical for cancer development and prognosis. There are many reports in the literature that increased neutrophil and platelet levels, indicative of systemic inflammatory response, are associated with tumor growth, invasion, angiogenesis and metastasis. Platelet increment has been shown to be associated with poor prognosis and poor survival in many types of cancer. As a result of our study, it was concluded that NLR, PLR, RDW and PDW levels of hemocytometer parameters do not have prognostic value in MTC.

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P1176

^{131}I-MIBG as a treatment in medullary thyroid carcinoma with distant metastases.

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Introduction and objectives
The strategies for therapy of metastatic medullary thyroid carcinoma (MTC) are limited. Although Tyrosine kinase inhibitors (TKI) seem to be the first-line treatment, we want to explore other possibilities. Metaiodobenzylguanidine (MIBG) is a guanethidine derivative, structurally similar to norepinephrine. It was developed as an imaging agent with ^{123}I radiolabeling. MIBG localizes neuroendocrine tumors including MTC. We are investigating the use of high doses of ^{131}I-MIBG as therapy for metastatic MTC. We present two case reports in which we used this therapeutic option.
Case reports
1) A 40-year-old woman, diagnosed at 26 of MCT with lymph node metastasis. She was surgically treated up to three times (due to lymph node recurrence). In 2015, there was an increase of calcitonin and CEA levels (1859 pg/dl, 27.1 ng/ml), showing metastases at lung, bone and breast. A ^{123}I-MIBG scan was performed, revealing an uptake of the radiotracer by bone lesions. One therapeutic dose of 200mCi ^{131}I-MIBG was administered, with uptake being appreciated by bone lesions but not by pulmonary lesions. After 6 months, the levels of calcitonin and CEA further raised (3353 pg/dl, 33.5 ng/ml). In the imaging study, an increase in the size of the pulmonary nodules was observed. TKI therapy was started.
2) A 39-year-old woman, diagnosed at 18 with endocrine neoplasia type 2B with CMT and bilateral pheochromocytoma, who underwent total thyroidectomy and bilateral adrenalectomy. In 2016, metastatic dissemination was observed with bone, liver and interaortocaval adenopathy lesions (calcitonin 10 279 pg/ml, CEA 64.7 ng/ml). It was treated with a high fractional dose of ^{131}I-MIBG (300 mCi, 360 mCi), with radiological progression of the disease in the hepatic parenchyma after 1 year. However, biochemical markers remained stable (calcitonin 9253 pg/ml, 85.6 ng/ml).
Conclusion
In our experience, the benefits of ^{131}I-MIBG therapy in metastatic medullary thyroid carcinoma are poor.

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P1177

Role of the fine-needle aspiration biopsy of cervical lymph nodes with thyreoglobulin washing tests in management patients with differentiate thyroid cancer.

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The aim of this study was the assessment of diagnostic utility of fine-needle aspiration biopsy needle washout fluids (FNAB-Tg) in the cases of thyroid carcinoma recurrence and analysis of false-positive and false-negative results.
Methods
Two hundred and fifteen FNAB-Tg samples from 201 patients with a history of differentiated thyroid carcinoma with suspicious lymph nodes were included in analysis. The wash-out of needle rinsed with 0.5ml of normal saline solution, using electrochemiluminescence method -ECLIA were performed.
Results
In 64 patients elevated FNAB-Tg levels correlated with positive cytology result. In 13 patients there were no correlation between elevated FNAB-Tg level and cytology result. Four of these patients had cystic metastasis of papillary carcinoma. Nine patients with metastases had not elevated FNAB-Tg levels. In four of them, FNAB revealed carcinoma cells from other malignancies. Three of patients had metastases of dedifferentiated thyroid carcinoma and two had differentiated thyroid carcinoma.
Conclusion
FNAB-Tg of the lymph nodes increases accuracy in the diagnosis of thyroid carcinoma recurrence, especially in detecting of cystic variants and micro-metastases or in coexisting malignances of other origin. False-negative FNAB-Tg results may occur in the cases of dedifferentiated thyroid carcinomas or with high serum anti-Tg antibodies.

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P1178

Malignancy risk stratification of thyroid nodules with cytological diagnosis of folicular neoplasm (Bethesda IV), according to the ultrasound sonographic patterns proposed by the American Thyroid Association (ATA)

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Background
The main limitation of fine-needle aspiration (FNA) is represented by indeterminate category (Bethesda III and IV) in which the risk of malignancy is between 5-30%. Given this result, surgical treatment is necessary in many cases. The aim of our study is to assess whether the ultrasound patterns proposed by the ATA, help us to stratify the risk of malignancy in nodules with Bethesda IV cytology result.
Methods
From January 2011 to June 2017 we selected all thyroid nodules referred to our Thyroid Unit, with cytological diagnosis of follicular neoplasia (Bethesda IV). All patients underwent surgical treatment. We retrospectively analyzed the clinical data (computerized clinical history) and ultrasound images. (All images were reviewed and classified in different ultrasound patterns by two endocrinologists with at least 5 years of experience in thyroid ultrasound.).
Results
A total of 263 nodules were selected with the following characteristics: Mean age ±S.D.: 52.1±15.1 years; sex: F/M (4/1); mean size of nodules 30.6±13.3 mm; TSH: 2.5 mU/L±8.6; thyroid autoimmunity 27.8%. The malignancy risk of the following ultrasound patterns is: Very low suspicion (0%), Low suspicion (16.7%), Intermediate Suspicion (27.9%) and High Suspicion (63.4%). 15 Nodules (5.7%) could not be classified within a specific pattern, presenting a risk of malignancy of 26.7%. Of the 263 nodules 68 were malignant (25.9%). 44 malignant nodules (64.7%) were papillary carcinomas, being the follicular variant the most frequent histologic type.
Conclusions
Ultrasound patterns proposed by the ATA, allow an adequate stratification of the malignancy risk, in nodules with Bethesda IV cytological results. This information may have clinical utility to decide the most appropriate surgical approach. However, 5.7% of the nodules could not be classified properly, presenting a risk of malignancy similar to those of Intermediate Suspicion.

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P1179

A rare case of mixed medullary and papillary thyroid carcinoma related with heterozygous VAL804MET mutationa rare case of mixed medullary and papillary thyroid carcinoma related with heterozygous VAL804MET mutation

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Introduction
Papillary thyroid carcinoma(PTC) and medullary thyroid carcinoma(MTC) have always been considered different tumors. Concomitant presence of MTC and PTC in the same patient is a rare clinical event.
Case report
A 43 year-old woman admitted with fatigue, a serum thyrotropin of 4.6 uIU/ml and a 15×11 mm thyroid nodule in right lobe detected in another center. Fine needle aspiration(FNA) of the nodule was consistent with MTC. In family history, her mother had thyroid cancer but the type was unknown. Repeat thyroid ultrasonography revealed a 14×11.8×18.4 mm solitary thyroid nodule in right lobe. There were also suspicious lymph nodes in right level VI and IV and left level IV. FNA along with tyroglobuline and calcitonin wash-out was performed to lymph nodes and thyroglobulin levels were 8423, 373.3 and 0.3 ng/ml respectively while calcitonin wash-out results were >2000 pg/ml in all lymph nodes. FNA cytologies were atypia of undetermined significance for the right and nondiagnostic for the left lymph nodes. Serum calcitonin was 655 pg/ml (<5 pg/ml) and carcinoembryonic antigen(CEA) was 45.1 ng/ml (0–3.4 ng/ml) . Evaluation for concomitant primary hyperparathyroidism and pheochromocytoma revealed no pathology. Total thyroidectomy with right lateral, left lateral and bilateral central lymph node dissection was performed. Pathology of the nodule was reported as 17×14 mm mixed medullary and papillary thyroid carcinoma'. Immunhistochemistry was positive for TTF-1 and calcitonin, and in focal areas thyroglobuline, CK-19 and HMBE-1 stainings were positive. One right lateral and three right central lymph node were tumour positive. The patient received 150 mCi radioactive iodine ablation therapy. Stimulated thyroglobuline was 4.2 ng/ml and a focal activity uptake in thyroid location was seen in postablative whole body scanning. Serum calcitonin and CEA regressed to 20.0 pg/ml and 2.7 ng/ml, respectively. The patient was heterozygote for C2410G>A (VAL804MET) mutation in RET protooncogene analysis. 26-year old daughter of the patient was also heterozygote for C2410G>A (VAL804MET) while other daughter had no mutation. Mutation carrier daughter of patient preferred active surveillance rather than prophylactic thyroidectomy.
Conclusion
Our patient is one of the rare cases of mixed medullary and papillary thyroid carcinoma that was evaluated completely both clinically and genetically. Mixed medullary and papillary thyroid carcinoma is a rare clinical entity but merits consideration in differential diagnosis of thyroid nodules particularly in patients with a family history of thyroid malignancy.

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P1180

Validity of sonographic pattern risk in thyroid nodules by the American Thyroid Association (ATA) and citological malignancy diagnosis

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Objetive
The aim of our study is to asses the validity of ultrasound patterns proposed by the ATA and malignancy risk in the cytological diagnosis classified by the Bethesda System.
Methods
Prospective study including all thyroid nodules (with no previous cytological results), assessed in our center from July/2016 to June/2017. We classified nodules in ATA sonographic risk patterns and follow-up its fine needle aspiration (FNA) recommendations. The statistical study has been carried out with the statistical package SPSS 20.0
Results
We evaluated 402 thyroid nodules. 160 were selected by ATA criteria to citologycal diagnosis. These correspond to 144 patients (80.2% women, mean age 52.8 years). Mean TSH was 1.82 (0.37–6.96) and 28.8% patients presented positive autoinmunity (antitiroglobulin and/or antiperoxidase antibodies). The mean size nodules was 2.8±1.2 cm, with those with lower ultrasound risk of malignancy being higher (3.2 vs 2.1 cm, P 0.02). The frequency distribution in the different sonographic risk categories were: High risk 16.3%, Intermediate risk 10.6%, Low risk 50%, and Very low risk 18.1%. The 5% of the nodules could not be classified in any of the previous patterns. The malignancy rates (according to Bethesda System Classification as malignant o suspicious for malignancy) in each sonographic group was: High risk 61.5%, Intermediate risk 5.9%, Low risk 0% and Very low risk 0%. Thyroidectomy was performed in 42 patients, 27 of them (64%) were thyroid carcinomas. The overall malignancy, including the histology in those patients surgically removed, correlates with the ultrasound data (P>0,001): 80.7% in High risk, 11% in Intermediate risk, 3.75% in Low risk and 0% in those with Very low risk. In non-classifiable nodules, malignancy was observed in 12.5%.
Conclusions
Our prospective results supports sonographic risk patterns of thyroid nodules and FNA recommendation proposed by ATA 2015 guidelines. We have found a highly correlation between each sonographic pattern and likelihood of malignancy, both in cytology and surgical histology.

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P1181

The role of thyroid imaging, reporting and data system scores – ACR TI-RADS in thyroid nodular disease – our expirience

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Introduction
The American College of Radiology proposed in 2017. ACR-TIRADS scoring system for the ultrasound findings of the thyroid gland. It now represents a standardized system of scoring pathological changes determined from five categories registered with ultrasound. High cumulative result leads to higher TR level and the higher probability of malignancy, which provides recommendations for eather FNA (fine needle aspiration) or further ultrasound monitoring of nodules assessed as most likely benign. The aim of the paper is to examine the relationship between ACR TI-RADS scoring system and the cytological findings obtained after the FNA which is represented by the Bethesda system.
Material and methods
Prior to each FNA, TI-RADS was calculated based on the ACR TI-RADS calculator, whereas the type of vascularization of the nodus and the perinodal tissue was determined. The study included 65 patients with the average age of 59 years and average TI-RADS of 3.43. From a total of 65 patients, 72% showed benign cytological finding, whereas 9% were in the AUS or AUS/FLUS category (atypia of undetermined significance/follicular lesion of undetermined significance). The remaining 19% of smears was non-diagnostic. None of the findings obtained had a suspect of malignancy. The average age of patients with benign finding was 58 years, and with AUS was 63 years. It was observed that for patients with AUS the average TI-RADS was 4, and that nodules were positioned in the right lobe, except in one case, where the position was in the area of isthmus. Average TI-RADS in nodules with benign pathohistological findings was 3.3, while 55% were positioned in the left lobe region.Only 6% of patients with benign findings had TI-RADS 1, 15% with TI-RADS 2, TI-RADS 3 had 28% and TI-RADS 4 had 40%, while TI-RADS 5 had 11% of patients. The group of patients with AUS was evenly allocated to results TI-RADS 3, TI-RADS 4, TI-RADS 5 each respresented with 33.3%. Vascularization of nodus type 2 had 34% and 8% had type 4 patient with benign findings,while with AUS findings, 50% of patients had type 2 and 0% type 4. By measuring the volume of nodules, and comparing them, it was found that the average nodus size was greater for patients with the AUS.
Conclusion
There are indications that the higher ACR TI-RADS was obtained in AUS cytological findings. Benign cytological findings were obtained in all TI-RADS 1 and 2.

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P1182

May cinacalcet improve psychiatric symptoms by decreasing calcium levels in lithium-associated hyperparathyroidism?

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Introduction
Lithium is the preferred and most efficacious therapy for acute and maintenance therapy of bipolar depressive disorder. Lithium use is associated with an increased incidence of hyperparathyroidism (4.3–6.3%) and have a female preponderance. Bilateral neck exploration was the most common surgical approach while a few patients were managed medically. The initial management of Lithium-associated hyperparathyroidism (LAH) is medical intervention which includes discontinuation of lithium or use of an alternative treatment such as atypical antipsychotics and calcimimetics. Here we demonstrate improved psychiatric symptoms after cessation of lithium and successful treatment of hypercalcemia by cinacalcet in a geriatric patient with LAH.
Case
81-year-old woman with a history of bipolar disorder treated with lithium carbonate for more than 10 years presented with nocturia and polyuria. Her serum calcium was 11.58 mg/dl (Normal – 9–10.5 mg/dl), alkaline phosphatase 175 U/L (Normal – 30–120 U/l)), serum parathyroid hormone 380 pg/ml (Normal – 10–60 pg/ml) and phosphorus 2.1 mg/dl (normal 3–4.5 mg/dl). No definite parathyroid lesions were identified by neck ultrasonography and Sestamibi/SPECT scans. Lithium treatment was stopped after consultation with psychiatrist. More than 3 months later, she had persistent hypercalcemia and depressive symtomps recurred. Cinacalcet (30 mg once daily) was started. After 2 weeks of treatment serum calcium level decreased to 9.5 mg/dl and PTH level was 160 pg/ml.Cinacalcet was well tolerated and the patient's psychiatric symptoms improved without any need for lithium or other antidepressant drug.
Conclusion
Cinacalcet is known to be effective in primary hyperparathyroidism but our observations also support the use of this calcimimetic agent in lithium-induced hyperparathyroidism as a potential alternative to surgery in geriatric patients. Treatment of hypercalcemia might help to resolve depressive symptoms in these patients. Cinacalcet could represent an important pharmacological intervention in MEN1-associated primary hyperparathyroidism before surgery and in post-surgical recurrences.

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P1183

Pediatric thyroid cancer is associated with more aggressive phenotype and more frequent RET/PTC rearrangements compared with the adult patients

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Thyroid cancer in children and adolescents is a rare disease but with an increasing incidence. As in adults, the most prevalent type is papillary thyroid carcinoma (PTC). Our aim was to describe the clinical and genetic comparison between pediatric and adult PTC. We analyzed the cohorts of 73 pediatric PTC (5-18 years, female to male ratio 2.3:1, 10 patients <10 years) and 460 adult PTC patients. DNA and RNA were extracted from cancer tissue samples. DNA was used for sequencing of *TERT* promotor C228T and C250T mutations with CEQ8000 and *BRAF* and *RAS* mutations by Nextera XT kit with MiSeq. RNA was used for detection of *RET/PTC1* and *RET/PTC3* rearrangements using Real Time PCR. Clinical and pathological data were compared between both cohorts. In the pediatric cohort, more aggressive categories T3 and T4 in TNM classification (47% vs 26.7%, $P=0.001$), significantly more frequent lymph node metastasis (73% vs 42%, $P<0.001$), extrathyroidal invasion (48.3% vs 29.9%, $P=0.007$) and angioinvasion (26.2% vs 14.0%, $P=0.026$) were present in comparison with adult PTC. The frequency of distant metastasis did not significantly differ between pediatric and adult PTC (4 vs 8.4%, $P=0.304$). Mutation in *RAS* genes was detected only in one patient - mutation Q61K in *N-RAS* gene (1,5% vs. 8% in adults, $P=0.065$), *BRAF* V600E mutation in nine pediatric patients (12.8% vs 37% in adult, $P<0.001$). No *TERT* mutations were found in pediatric PTC in contrast to 12% in adults ($P=0.004$). *RET/PTC* rearrangements were found in 14 patients (20.9% vs 5% in adults, $P<0.001$) – nine RET/PTC1, five *RET/PTC3* and one *RET/PTC1ex9* were detected. *RET/PTC1ex9* in 8 years old boy with aggressive classical variant of PTC (T4N1M1) was created by fusion of exon 1 of CCDC6 with exon 9 of extracellular domain of *RET* followed by exon 12 of RET. One 17 years old patient with T3N1M0 had *BRAF* V600E mutation together with RET/PTC1. In our cohort, PTC in pediatric patients presented more aggressive features than in adults, mainly with more advanced T in TNM classification, more frequent lymph node metastasis, extrathyroidal extension and angioinvasion. The molecular genetic analysis revealed that the prevalence of the *RET/PTC* fused genes was significantly higher in pediatric PTC compared with adult PTC, in contrast to significantly lower prevalence of the *BRAF* V600E and *TERT* mutations.

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P1184

Serum osteopontin levels in newly diagnosed thyroid cancers

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Purpose
Thyroid cancer is the most common cancer of endocrine system. Osteopontin (OPN) is a secreted glycoprotein that has a role in osteoblast differentiation and bone formation. Osteopontin has other roles in cell migration and cell survival and its related to tumorigenesis and cell invasion. Osteopontin levels have been determined higher in some malignancies. The purpose of this study is to determine plasma osteopontin levels in patients with new onset diagnosed thyroid cancer and to compare them with plasma osteopontin levels in healthy people.
Method
In our study we planned to compare two groups. The first group was composed of patients with newly diagnosed differentiated thyroid cancer (40 patients) and the second group was composed of healthy individuals (40 patients). Blood samples (5 ml) for osteopontin were collected for both groups, centrifuged and frozen at −80 °C. Osteopontin levels were studied with ELISA method at once.
Findings
OPN levels were determined 10.21 ± 3.67 ng/ml in patients and 6.14 ± 2.29 ng/ml in control group. OPN was determined higher in patients and this difference was statistically significant ($P < 0.001$). There was no significant correlation between OPN level and prognosis and aggressiveness.
Results
OPN levels were higher in patients with thyroid cancer. This case was associated with pathophysiological role of OPN in tumorigenesis. OPN levels were not significant in predicting prognosis and aggressiveness. Further studies are needed to be understood the role and importance of OPN.

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P1185

First report of c.1683A > G *FLT3* mutation found in the follicular thyroid cancer

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Introduction
The number of thyroid cancer diagnosis has increased worldwide. However, its diagnosis, particularly in a case of follicular cancer (FTC), may be challenging. New markers of malignancy are intensively searched for.
Case description
A 29-year-old female was referred for subtotal thyroidectomy in 2006 due to a nodule in the right lobe. The histopathological examination revealed follicular adenoma (FA). During endocrinological follow-up, in 2008 a local recurrence in the thyroid bed and the presence of metastases to the lymph nodes and lungs were observed. Thus, the patient was referred for total thyroidectomy and lymphadenectomy. Histopathological examination of the resected specimen demonstrated the presence of FTC. Due to persistent disease, the patient required two subsequent lymphadenectomies followed by radioiodine therapy. However, the result of the therapy was unsatisfactory. Consultation of the material acquired from the first surgery resulted in conclusion that, taking into account the clinical course of the disease and morphological similarity of weaving in both histopathological specimen, the nodule in the right thyroid lobe operated in 2006 was presumably a FTC. Patient has been subsequently treated by lenvatinib from 2012 to 2015 acquiring total structural and partial biochemical remission. The drug was withdrawn due to the disease recurrence. Patient was reoperated in 2015 and has been treated with sorafenib since 2016. However, the remission of the disease has not been achieved until now. The histopathological specimen from the first surgery has been prepared for next-generation sequencing. DNA was acquired from histopathological slide. NGS sequencing was done on the *Ion PGM Sequencer (Thermo Fisher,* USA) employing *Ion AmpliSeq Comprehensive Cancer Panel*. The obtained data from genomic experiments were subjected for analysis using dedicated software. The analysis revealed the presence of fms-related tyrosine kinase 3 (*FLT3*) mutation on chromosome 13 – c.1683A > G (COSM19740), silent substitution present in coding region, position 561 L → L. The occurrence of the mutation has not been confirmed in the patient's leucocyte DNA through NGS, which confirms its somatic character.
Conclusions
Although *FLT3* has been previously reported in hematological malignancies, such as acute myeloid leukemia or myelodysplastic syndrome, to the best of our knowledge this is the first report of the presence of *FLT3* mutation in the thyroid tissue. Due to diagnostic problems in a case of our patient, finding a new marker of FTC and possible prognostic factor is crucial, what might be the basis for new targeted therapeutic options.

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P1186

Thyroglossal duct cyst papillary carcinoma: case report and review of literature

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Objective
To report a rare case of papillary thyroid carcinoma (PTC) in a thyroglossal duct cyst (TGDC).
Case report
A 34-year-old peruvian male came to our hospital with a complaint of a swelling cervical mass in the anterior central side of the neck, which was growing since 6 months earlier. The patient had no significant past medical, surgical history and was completely asymptomatic. He denied any family history of thyroid disease or history of head and neck irradiation. Physical exam reveal a nontender, not much mobile and semi-solid neck mass measuring 5 cm in the suprahyoid median line, with some phlogosis signs. Laboratory examinations include: TSH 3.21 uIU/ml, T4L 1.0 ng/dl and Anti-TPO/AbTg (-). Cervical ultrasonography revealed homogenous thyroid gland with normal dimensions. RTL: hypoechogenic nodule with defined edges of 9×7 mm soft consistency to elastography. In the anterior central side of the neck, suprahyoid cystic image with sediment and thick calcifications was observed, measuring $48 \times 39 \times 59$ mm, with a volumen of 58.5 cc. CT: encapsulated, lobulated and bilobed cystic lesion with small internal calcifications measuring $33 \times 30 \times 15$ mm, located in the midline cervical, as well as multiple cervical lymph nodes enlargement, the largest in the right carotid side. FNAB of cervical tumor: malignant neoplasm of papillary aspect of probable thyroid origin. Sistrunk procedure was performed, during which we found a 7 cm mass, with necrosis of the anterior side and thinning of the skin, as well as a superficial pre-laryngeal lymph node. Histopathology of the mass demostrated a PTC papillary and follicular variant in TGDC, with infiltrative borders and capsular and bone invasion, measuring in greatest dimension 1 cm, excision margins free of neoplasia. Presence of neoplasic invasion of lymphatic vessels. Lymph node and submental region free of neoplasia. Patient underwent a total thyroidectomy that reported absence of malignant lesion. Patient is waiting for ablative radioiodine.
Conclusion
The clinical presentation of PTC in the TGDC in the early phase; It presents an anterior cervical mass of rapid grow, fixed, indurated, irregular, accompanied by lymphadenopathies in the upper jugular group. The role of total thyroidectomy is still controversial, as is postoperative adjuvant treatment. The prognosis of PTC of the TGDC is good.

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P1187

Thyroid imaging reporting and data system: how useful is it in distinguishing follicular adenomas from follicular carcinomas?

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Introduction
Various thyroid imaging reporting and data systems (TIRADS) have been proposed in recent years, such as the EU-TIRADS proposed by the European Thyroid Association (ETA). These classification systems intend to estimate the malignancy risk of thyroid nodules, however they are very much based on suspicious ultrasound (US) features typical of papillary thyroid cancer. As such, follicular carcinomas may be reported as low suspicion nodules. Our work aims to evaluate the performance of the EU-TIRADS in follicular neoplasms and how

accurate are their ultrasound high suspicion features in distinguishing follicular and Hürthle cell adenomas from carcinomas.
Methods
Retrospective study including patients followed-up in a Portuguese central hospital for the past 10 years who underwent to thyroid surgery and received subsequent histological diagnosis of follicular carcinoma, follicular adenoma, Hürthle cell carcinoma or Hürthle cell adenoma – 151 patients. We identified every patient who had US imagological records from before surgery available for review. The US features were retrospectively evaluated and the nodules were classified according to their EU-TIRADS score.
Results
We included 39 patients with histological diagnosis of follicular neoplasm (18 malignant) – seven follicular carcinomas, 16 follicular adenomas, 11 Hürthle cell carcinomas and five Hürthle cell adenomas. The mean age at surgery was 55 ± 14 years and 74% of patients were female. The mean nodule diameter was 31 mm (adenomas: 29 mm and carcinomas: 34 mm, $P = 0.260$). The presence of a hypoechoic halo was associated ($P = 0.034$) with increased odds of benign nodule etiology. No statistically significant differences were identified regarding nodular composition, shape, margins or existence of microcalcifications between carcinomas and adenomas. Both adenomas and carcinomas had EU-TIRADS score of 3 (benign: 8, malignant: 4), 4 (benign: 6, malignant: 8) or 5 (benign: 7, malignant: 6) and this distribution did not reach a statistically significant difference ($P = 0.479$). EU-TIRADS category four had the highest sensitivity for detecting malignant lesions – 44.4%. Most malignant ($n = 12$) and benign ($n = 14$) nodules did not present any EU-TIRADS high suspicion US features and the number of features was not statistically significantly different between carcinomas and adenomas ($P = 0.208$). Only 1 malignant nodule did not have an EU-TIRADS score and diameter that would imply fine-needle aspiration (FNA) according to ETA EU-TIRADS guidelines.
Conclusion
EU-TIRADS based high suspicion US features do not seem valuable in distinguishing follicular adenomas from carcinomas. Nevertheless, the majority of carcinomas scored as EU-TIRADS category 4 and 5 – intermediate and high-risk categories which should warrant FNA in most cases.

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P1188

Descriptive study about clinical and surgical characteristics of patients with differentiated thyroid cancer in our health area

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Introduction, material and methods
Differentiated thyroid cancer is a pretty common reason for consulting in our specialty. In general terms, the prognosis is good in the main histological type but there are many others that can worsen the prognosis. It can determine the kind of surgery from hemithyroidectomy (e.g. microcarcinoma) to no intervention because of its extension at the moment of diagnosis. We have collected the data of our patients with differentiated thyroid cancer during the period from 2000 to 2015 and we have described the epidemiological, pathological and surgical aspects of them and compared with the rest of the main series published. Statistical analysis was made with Stata.
Results
A total amount of 87 valid cases of thyroid cancer were diagnosed during the period from 2000 to 2015. The average age was 46.16 (95% CI, 42.76–49.55). From these cases, 72 were female (83.0%) and 15 were male (17.24%). Diagnosis with FNA before surgery showed: 30 (34.88%) were Bethesda 2, 29 (33.72%) were Bethesda 5, 13(15.12%) were Bethesda 3 or 4, 6 (6.98%) were Bethesda 1 and in 8 (9.3%), FNA was not made. About surgery, they underwent to: 65 (74.71%) total thyroidectomy, 1 (1.15%) near-total thyroidectomy, 3 (3.45%) hemithyroidectomy, 17(19.54%) total thyroidectomy in two periods and 1 (1.15%) did not have thyroid surgery; 47(54.02%) were underwent lymphadenectomy and 40(45.98%) were not. About histological type, 80 (91.55%) were papillary thyroid cancer and 8 (8.05%) were follicular thyroid cancer. About histological subtype: 28 (36.44%) were classical forms, 14 (18.42%) were microcarcinoma subtype, 25 (32.89%) were follicular subtype, 3 (3.95%) were encapsulated subtype, 2 (2.63%) were tall cell variant, 1 (1.32%) was diffuse sclerosing variant, 1 (1.32%) was Hürthle papillary carcinoma, 1 (1.32%) was minimally invasive follicular carcinoma and 1 (1.32%) was invasive follicular carcinoma.
Conclusions
We can confirm that thyroid cancer is presented predominantly in women at a young age. Also, we can appreciate the low sensitivity of the FNA in our centre. Total thyroidectomy (in 1 or 2 periods) is the most usual technique for the thyroid surgery, leaving hemithyroidectomy for micropapillary thyroid cancer and conservative treatment for unresectable cases. The most frequent histological type is papillary thyroid cancer and within this, the classical form. Based on our data, we can say that our results are similar to the main series published (except in some fields as the FNA results).

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P1189

Thyroid ultrasonography and fine needle aspiration: a center experience

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Introduction
Thyroid ultrasonography and fine needle aspiration (FNA) are the most useful techniques in the evaluation of thyroid nodules. They are cheap, fast, minimally invasive and high precision methods. The FNA can be performed by palpation or ultrasound guidance. The use of ultrasound reduces the nondiagnostic results rate. However, the cytologic diagnostic accuracy depends on the technique and pathologist experience. Ultrasonography confirms the presence of a thyroid nodule, its precise location and the presence of other nodules not yet known; allows to characterize thyroid nodules, detect lymph nodes and screen high risk patients for thyroid malignancy. In Portugal, thyroid ultrasonography and ultrasound guided-FNA (US-FNA) were performed by radiologists but now are performed by endocrinologists too. The Endocrinology department of Coimbra Hospital was one of the pioneers, with experience since 2005.
Objective
The objective of this study is to show the experience of a center, that performs thyroid ultrasonography and US-FNA.
Material and methods
Review and statistical analysis of all thyroid ultrasonographies, US-FNA and histologic results, performed in the Endocrinology department of Coimbra Hospital, between January 1, 2017 and October 31, 2017.
Results and conclusion
Between January 1, 2017 and October 31, 2017: 381 ultrasonographies (without FNAB) and 1452 US-FNA.Total number of patient: 1517. Average age: 58.4 years (s.d.: 14.9 years). Younger patient: 10 years. Older patient: 91 years. Total number of women: 1250 (82%) and men: 266 (18%). Nondiagnostic/unsatisfactory results rate low (1.,8%). The most of histologic results was *benign* – class II of Bethesda Classification (80.8%). Other results*:* FLUS – a*typia* of undetermined significance or follicular lesion of undetermined significance (Bethesda III): 10.5%; follicular neoplasm or suspicious for a follicular neoplasm (Bethesda IV): 4.7%; Suspicious for papillary carcinoma (Bethesda V): 1.1%. Papillary thyroid carcinoma (Bethesda VI)*:* 1.3%. The complication rate was null. Thyroid ultrasonography and US-FNA are useful tools in the evaluation and management of thyroid disorders. It should be performed in all endocrinology departments. The benefit of this practice depends on the clinical endocrinologist experience and continuous training helps decision-making. Molecular studies will be helpful in elucidating indeterminate results – FLUS and follicular tumour.

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P1190

Brain metastases from papillary thyroid carcinoma, 31 years later

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Introduction
Papillary thyroid carcinoma (PTC) is a differentiated thyroid carcinoma and is the most common variant. It is more frequent in women and the median age at diagnosis is 45 years. Most PTC are clinically indolent, have a good prognosis and

low incidence of distant metastases. The more frequent locals of distant metastases are bone and lung. Brain metastases are very rare and associated with a poor prognosis.
Case report
We present a case of a 74-years-old woman, without history of radiation and no family history of thyroid disease. In 1984, she underwent a total thyroidectomy with cervical lymphadenectomy. The histologic result was a *papillary thyroid carcinoma,* with cervical *lymph node and pulmonary metastases* (T4bN1M1). Between 1984 and 1999, she realized multiple doses of therapeutic radioiodine – I^{131} (cumulative dose $>$1Ci). After the last treatment (1999) she realized a post-therapeutic scan that showed no significant uptake (although she maintains pulmonary metastases – clinically indolent). At 2009 she underwent a thoracotomy (nodule with 12 mm). The histologic result was a papillary carcinoma metastase. In 2012 the 18FDG-PET showed bilateral pulmonary metastases with some dedifferentiated lesions. The follow-up showed stable values of thyroglobulin (Tg: 32–57 ng/ml, TgAb: negatives). In November, 2015, she developed a behavior change and realized a cranial CT: frontal lesion with 55$\times$26 mm. December, 2015: she underwent a total excision of the brain lesion; histology: brain metastases from papillary thyroid carcinoma. 18FDG-PET (February, 2016): no hypermetabolic lesions suggestive of dedifferentiated lesions. July, 2016: recurrence of the frontal/temporal brain metastase (50 mm). She realized a second surgery; histology: brain metastase. She underwent holocranian radiotherapy (30Gy) and started Sorafenib (October, 2016). Despite this, there was progression of brain lesions and she developed adverse effects. It was decided stop sorafenib. The patient maintains oncology and neurosurgery visits.
Discussion and conclusion
The present case show that brain metastases, although rare, can occur decades after the diagnosis of papillary thyroid carcinoma. Surgery and radiotherapy are the main therapeutics approach. Tyrosine kinase inhibitors was approved by FDA for the treatment of patients with radioiodine-refractory metastatic thyroid cancer, but the experience is limited. Patients with brain metastases have a poor prognosis.

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P1191

Ectopic thyroid tissue challenge: clinical case report

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Introduction
Ectopic thyroid tissue is a rare embryonic developmental defect that occurs during the thyroid transition from its initial position in the floor of the primitive bowel to a pre-tracheal location. This defect has a prevalence in the general population of 0.3–1/100,000 inhabitants, increasing to 0.5–1/4,000 patients with thyroid pathology. It is more common in women and can be diagnosed at any age, with diagnosis being more common in young individuals.
Clinical case
A 78-year-old woman, referred to our department in September 2017 had complaints of hoarseness and choking with 2 months of evolution. The patient had history of nodular thyroid disease, with total thyroidectomy when she was 18 years old. At age 73, after diagnosis of ectopic thyroid, she underwent partial excision of thyroid tissue from the base of the tongue and anterior cervical region, which revealed Papillary Microcarcinoma. On physical examination it was observed a recurrence of the lesion at the base of the tongue with a nodule of 21$\times$18$\times$17 mm, for which subtotal removal of this region was performed. Histology of the surgical specimen revealed unchanged ectopic thyroid tissue.
Discussion/conclusion
The base of the tongue is the most frequent location of ectopic thyroid tissue, with a prevalence of 90% of all cases reported. The most frequent clinical presentation includes complaints of dysphagia and dysphonia, foreign body sensation, cough and airway compression symptoms that occur with a mean age of 40.5 years. Primary carcinomas of ectopic thyroid tissue are uncommon, with diagnosis of lingual thyroid tissue, thyroglossal ductal cyst, mediastinum, and ovary. They are usually diagnosed only after excision of the lesion, with a more frequently papillary pattern. However, follicular, mixed, Hurtle and medullary patterns are also reported. The approach of these malignant lesions is similar to those of thyroid origin, although the presence of ectopic thyroid tissue may be a therapeutic challenge, both in the surgical approach and in the adjustment of levothyroxine doses.

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P1192

Tyrosine kinase inhibitors in iodine-refractory thyroid cancer. Clinical experience

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Introduction
Tyrosine kinase inhibitors (TKIs) are used for treatment of iodine-refractory differentiated thyroid cancer (DTC) in patients with progressive advanced disease.Sorafenib and lenvatinib are the TKIs currently approved for this indication.
Objective
To describe the clinical experience in patients with iodine-refractory DTC treated with TKIs in our Institution.
Materials and methods
Restrospective cohort study of patients with iodine-refractory DTC who received TKIs from 2010 to 2017 in Hospital Universitario La Princesa.We included patients with available clinical data and at least one radiographic control after starting treatment with TKIs.Patients with anaplastic or medullary thyroid carcinoma were excluded.Baseline clinical characteristics, evolution, objective response to treatment, tolerability and adverse events(AE) were collected.Data were analyzed by descriptive statistics with G-Stat 2.0.1.
Results
Twelve patients were included. Mean age at diagnosis was 54(SD13.7) years, (83.3% women). Histhologic diagnosis: 7 papillary thyroid cancer, 4 poorly differentiated follicular thyroid cancinoma and 1 Hürtlhe cell cancer. Distant metastasis at diagnosis were present in 25% of patients. In the other 75% median time to metastasis diagnosis was 24(IQR12) months. Seven patients had more than one metastatatic lesion site. Median time from diagnosis of distant metastasis to TKIs initiation was 24(IQR78) months. Sorafenib, lenvatinib and sunitinib were used as first-line treatment in 8, 2 and 2 patients respectively. First radiographic control was performed at 5.33 (SD2.7) months after start of treatment and showed partial response(PR), stable disease(SD), complete response(CR) and progressive disease(PD) in 5(41.67%), 1 (8.33%), 1(8.33%) and 5(41.67%) patients respectively, with an objective response rate of 58.3%. The only CR was seen on first-line lenvatinib. Before radiographic control 2 patients required a second-line treatment with sorafenib and sunitinib each, due to intolerability. AE occurred in all patients. The most common were fatigue/hyporexia (83.3%) followed by cutaneous AE (58.3%), diarrhea (41.6%), hypertension (16.6%) and mucositis (16.6%). Cutaneous AE ocurred only with sorafenib. The rest of AE were collected for all TKIs (including one case of grade 3 mucositis with Lenvatinib). All patients eventually required dose reductions due to toxicity. Definitive withdrawal was necessary in 83.33% of patients, 50% due to toxicity and 33.33% due to progressive disease. Mortality related to cancer occurred in 8 patients, with a median time of 18 (IQR36) months after start of TKIs.
Conclusion
In our study, use of TKIs showed a similar clinical response to reported in literature with sorafenib. AE are common, being necessary a multidisciplinary management of this treatment in specialized centers.

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P1193

Correlation between TSH level and benignity and malignancy of thyroid nodules (about 250 cases)

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Background
Plasma TSH is a fundamental marker of thyroid function. The TSH level might be different depending on nodule's type. Recent studies have shown a relationship between plasma TSH levels and thyroid nodules malignancy. The aim of this study was to compare the TSH level between two groups of subjects who had undergone total thyroidectomy, one group whose final histology was benign and one group who had a malignant histology.
Materials and methods
It was a retrospective study including 250 patients followed in Endocrinology department of bn Rochd University Hospital of Casablanca between 2012 and 2017, for nodule or multinodular goitre, having undergone surgery. Two groups of patients were compared according to the level of TSH: 1/3 higher, 1/3 medium

and 1/3 lower. Different variables were studied such as age, gender, family history of thyroid disease. Statistical analysis performed by the software SPSS.16.
Results
Mean age of the patients was 41 years (18-71 years), with a female predominance (92%). Familial thyropathy was present in 32% of cases. Surgical indicated was in front of the nodule size in 46% of the cases, the toxic character (23%) and the suspicion of malignancy in 25% of the cases. All patients were preoperatively on euthyroidism. Histology was benign in 68% of cases and malignant in 32% of cases. There was no significant difference between the two groups in terms of age, gender, family history of thyroid disease, or thyroid autoimmunity. Subjects whose final histology was malignant had a mean level of TSH significantly higher than subjects with benign disease (2.98 mU/l versus 0.96mU/l, $P=0.003$). Cancer risk was significantly greater when TSH was in the upper tertile of normal range ($P<0.001$)
Conclusion
These data confirm a higher level of TSH values in subjects with thyroid cancer. However, it seems difficult to define a threshold that would allow to know preoperatively if the nodule is benign or malignant.

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P1194

Efficacy and toxicity of lenvatinib treatment for radioiodine refractory thyroid cancer in daily clinical practice: a single centre experience

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Introduction
Lenvatinib is a multitarget tyrosine kinase inhibitor that has shown substantial efficacy in patients with progressive radioiodine refractory thyroid cancer (RAIRDTC) (progression free survival (PFS) 19.4 months and objective response rate 64.8%; SELECT trial) despite common adverse events (AEs).
Objective
To evaluate efficacy and toxicity of lenvatinib treatment for RAIRDTC in daily clinical practice.
Methods
Retrospective clinical record review of 12 RAIRDTC patients treated with lenvatinib from April 2015 to December 2017 in our hospital.
Results
Twelve patients were analyzed (4 females, median age 62 years (range, 47-82)). Every patient had distant metastasis (83% lung, 67% bone, 58% lymph nodes, 25% liver) and 11 out of 12 had evidence of progressive disease (PD) within 6 months prior to lenvatinib start. Only 4 patients received lenvatinib as first line treatment (range, $1^{st}-6^{th}$ line). Initial dose was 24 mg in 11 out of 12 patients and 10 mg in 1 patient (82 years, ECOG 3, several comorbidities). Median follow-up (duration of treatment) was 14.9 months [0.3-33.5]. Median PFS was 24.3 months (CI 14.7 - 33.8) although data are immature since only 4 patients had progressed at the time of analysis. In 2 patients lenvatinib was not stopped despite PD; both show stable disease at last follow up (6.1 and 3.1 months after first progression). 4 of the 8 patients (50%) in which evaluation of tumour response was available achieved a partial response; 4 (50%) stable disease. No complete responses were observed. All patients presented grade 3 (G3) or superior AEs. The most frequent AEs related to treatment were fatigue (100%; 16% G3), hypertension (83%; 83% G3), nausea (75%; 8% G3), weight loss (67%; 8% G3), diarrhea (50%; 0% G3), arthralgia (50%, 0% G3), mucositis (33%; 0% G3), hand-foot syndrome (25%; 0% G3) and proteinuria (17%, 0% G3). Seven (58%) and ten (83%) patients had dose reductions or interruption of lenvatinib due to AEs. Median time to dose reduction or interruption was 1.9 months. Most dose interruptions were very brief (median duration 2 days). Median dose at last follow-up was 14.9 mg/d (range 7.1 – 24 mg/d). Two deaths occurred, one considered to be drug related (bleeding during cervical abscess surgery).
Conclusion
Remarkable benefit of lenvatinib treatment for RAIRDTC is achieved in daily clinical practice. Our results, in heavily pretreated patients, are in agreement with those of the SELECT trial. AEs are frequent and require close management and dose titration.

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P1195

Comparative study about clinical characteristics at the moment of surgery and follow-up depending of histological type in patients with differentiated thyroid cancer in our health area

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Introduction, material and methods
Papillary thyroid cancer is well known to be a tumour with a good prognosis; in spite of that, it usually presents many recurrences that increases its morbidity. Follicular thyroid cancer is less frequent but has a higher rate of hematogenous dissemination and higher mortality than papillary thyroid cancer. We have collected the data of our patients with differentiated thyroid cancer during the period from 2000 to 2015. In this study, we have described the clinical and follow-up aspects of these patients and compared them depending if the patient was affected of papillary or follicular thyroid cancer. Clinical differences were measured trough odds ratio (OR) when possible. Statistical differences were measured through OR's confidence interval when possible, and Fisher's exact proof when OR was not possible. Papillary thyroid cancer was considered the category of reference. Statistical analysis of the data was made with Stata IC 14.2.
Results
A total amount of 87 valid cases of thyroid cancer were diagnosed during the period from 2000 to 2015. From the total amount of the cases, 80(91,95%) were papillary thyroid cancer and 7(8,05%) were follicular thyroid cancer. Comparing the follicular cases with the papillary, there were clinical and statistically significant differences in distant metastasis at the moment of diagnosis [OR 18.5 (CI 95% 1.74-176.8). There were also statistically significant differences in AJC7 classification (Fisher's exact $=0.002$), ATA risk classification (Fisher's exact $=0.006$), number of radioiodine sessions (Fisher's exact $=0.031$) and death because of thyroid cancer (Fisher's exact $=0.006$). There were no statistically significant differences in the rest of categories analysed: age, sex; multifocality, lymphadenopathies or extrathyroidal involvement in the moment of diagnosis; treatment with radioiodine and presence of antithyroglobulin antibodies.
Conclusions
We can confirm that patients affected of follicular thyroid cancer are more aggressive in the moment of diagnosis and have worse prognosis during the follow up with higher risk of death. We recognize two main limitations in this study: the first would be the few cases of follicular thyroid cancer in our data that can subtract power from the study; the second one would be that our study is a raw analysis and there may be confounding factors that interfere with the results of our study.

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P1196

Insular carcinoma of the thyroid diagnostic and prognostic evaluation

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Background
Insular carcinoma of the thyroid is an extremely rare tumor (4% of cases) with a poor prognosis and an intermediate malignancy between differentiated and anaplastic cancers. The aim of this study was to define the particular points of this cancer by studying its diagnostic and prognostic aspects.
Materiel et methods
Retrospective study was conducted in Endocrinology and diabetology department of Ibn Rochd University Hospital of Casablanca, including 14patients followed for insular thyroid carcinoma between 1986 and 2017 among all thyroid carcinomas (614 patients)
Results
Insular carcinoma prevalence was 2%. Mean age was 56 (18-71)years. Reason for consultation was goiter in 9 patients and an isolated nodule in 5 patients. All patients had undergone total thyroidectomy with lymphnode dissection. Iratherapy (100 mci) was performed in all patients. Insular carcinoma represented the total tumor in 3 cases, or was associated with a well-differentiated follicular (3 cases) or papillary (8 cases) contingent. The mean size tumor was 4 cm (2–8 cm). Histological stages (pTNM) wereT2 (9 cases) T3 (3 cases) T4 (2 cases)

N0 (10 cases) N1 (4 cases). A recurrence was found in 2 patients (locoregional recurrence and bone metastasis) with a delay of 28 months. Predictors of poor prognosis were age, large size, multifocality, and capsule invasion ($P<0.01$).
Conclusion
Our results highlight the rarity of insular carcinoma with a potential severity (pTNM stage, frequency of recurrence).

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P1197

Amiodarone – thyrotoxicosis and thyroid cancer

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Introduction
Although thyrotoxicosis is considered to be a very rare finding in a patient with thyroid cancer, there are several reports regarding this unexpected association in specialty literature. A frequent cause of thyrotoxicosis in patients with cardiac disease is amiodarone-induced thyroid dysfunction. The mechanism underlying this adverse reaction can be attributed to high iodine content and the direct toxic effect of the drug on thyroid cells.
Case report
We present the case of a male patient, age 69, treated with amiodarone for paroxistic atrial fibrillation, which addressed our service for a large anterior cervical mass which was observed by the patient two months before presentation. Initial laboratory evaluation revealed thyrotoxicosis and the neck ultrasound revealed a very large anterior cervical hypoechoic mass which appeared of thyroid origin and which extended to the submandibular region and retrosternal. The contrast CT scan of the neck, thorax and abdomen revealed large non-homogenous thyroid mass extended cervical and thoraco-mediastinal with sternal invasion and bilateral pulmonary nodules. The fine needle aspiration and the immunohistochemistry results where consistent with undifferentiated thyroid carcinoma. The I131 scintigraphy of the thyroid revealed non-homogeneous distribution of I131 with areas with no captation in both thyroid lobes. The patient underwent external radiation therapy and chemotherapy. Since 09.2017, he was started on sorafenib and now is on substitutive treatment with levothyroxine.
Conclusions
There are few cases reported in specialty literature of undifferentiated thyroid cancer in patient with amiodarone therapy, but the question whether this rare finding is influenced by high iodine content in the antiarrhythmic drug is still unanswered.

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P1198

Thyroid carcinoma in adolescents and young adults (about 120 cases)

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Background
Differentiated adolescent and young adult thyroid cancers are under diagnosed. They would be characterized by their aggressiveness and the presence of particular histological forms. The aim of the study was to define the particular points of thyroid carcinoma in this population by analyzing the clinical, histological and therapeutic characteristics.
Materials and methods
A case-control study was conducted in the endocrinology and diabetology department of Ibn Rochd University Hospital of Casablanca between 1986-2017, including 120 cases of thyroid cancer in young adults < 25 years old. The control group included 290 patients followed for thyroid carcinoma and aged between 25 and 60 years. Statistical analysis performed by the software SPSS.16
Results
Mean age of our patients was 19.3 years (15-25 years).Family history of thyroid carcinoma was found in 10 patients. The predominant mode of discovery was an isolated nodule in 67% of cases. All patients underwent total thyroidectomy with lymphnode dissection in 25% of cases. Papillary carcinoma was the histological type in all cases of young adults. Recurrences were found in 7% of cases, (locoregional recurrence (5%) and pulmonary metastases (2%) with a mean delay of 18 months. Analytical study showed that the prognostic factors as multifocality, capsular invasion and extra-thyroid extension, were significantly higher in the young group compared to the control group and that the metastasis were earlier.
Conclusion
Differentiated cancers of the young subject are more frequent and invasive. Precocity and frequency of local and distant metastases are an evidence of particularly aggressive forms as reported in the literature.

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P1199

Anaplastic thyroid cancer: a diagnostic and therapeutic challenge

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Introduction
Thyroid cancer incidence has registered an important increase in the last years. Anaplastic thyroid cancer represent a rare malignancy with an aggressive biological behavior and a high mortality rate.
Case presentation
We present the case of a 69-years-old woman who addressed our department for endocrine evaluation in the context of a right latero-cervical lymph nodes, complaining of mixed dysphagia and dyspnea, that developed progressively over the last month. The patient associates essential hypertension and mixed dyslipidemia under treatment. Thyroid functional hormone profile indicated subclinical hyperthyroidism with suppressed TSH = 0.09 mUI/L (N = 0.5-4.5 mUI/L) and normal values for free thyroxine (FT4) and triiodothyronine (T3) of 21 pmol/l and 160ng/dl. In addition, normal calcitonin and carcinoembryonic antigen values were registered. The thyroid ultrasound performed showed a right thyroid lobe completely occupied by a hypoecogenic macronodule, apparently non-vascularized, of 6.3/5.5 cm, and a left thyroid lobe with a hypoecogenic macronodule of 2.5/1.6 cm. In the right supraclavicular region there were described multiple adenopathies, the largest with internal Doppler signal of 3.97/2.8 cm and superior to it other suspicious adenopathies of 1.31/1.04, 0.7/0.65 cm and 0.8/0.6 cm. The computer tomography scan of the cervical, thoracic, and abdominal regions with contrast enhancement have identified a large thyroid process with micro and macro-calcifications in the interior, extending in the posterior, moving laterally the esophagus and the trachea with dimensions of 4.28/6 cm. Also, a right adenopathic laterocervical process of 3.9/3 cm in the right supraclavicular fossa, multiple bilateral pulmonary nodules with a maximum diameter of 3 cm and multiple right pleural nodules with a maximum diameter of 2 cm (metastatic determinations). The patient was referred to surgery department, where surgical resection was attempted and a tracheotomy was performed. The histopathologic examination confirmed the anaplastic thyroid cancer. Subsequently, the patient was addressed to the oncology service where she started loco-regional radiation therapy, taking into account the association of chemotherapy with doxorubicin and cisplatin regimens.
Conclusions
Case of a patient diagnosed with metastatic anaplastic thyroid cancer (stage IV c) for whom prognosis is reserved.

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P1200

RET exon 11 genotype in medullary thyroid cancer

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Introduction
RET mutation is a well-known pathogenic event in medullary thyroid cancer. However, less than 25% of MTC cases present a germline mutation. First grade relatives of the patients with germline RET mutations may undergo genetic counselling and prophylactic appropriate therapeutic intervention.

Objective
The aim of the study was to evaluate the most frequent pathogenic RET exon 11 mutations and SNP in medullary thyroid cancer (MTC).
Patients and methods
A consecutive case series of 41 patients (30F, 11M) with confirmed MTC was submitted to genomic DNA sequencing for RET mutation. A number of 12 cases were included in familial syndromes (5 families), mostly MEN2A. Six of them were screened due to their affected relatives. Genomic DNA was isolated from EDTA-treated blood, using Promega Wizard Genomic DNA Purification Kit. Exon 11 of RET gene was amplified in a fragment of 419 bp, by polymerase chain reaction (PCR)using forward (ATACGCAGCCTGTACCCAGT) and reverse (CACAGGATGGCCTCTGTCTC) primers. Cycling conditions: 95° C for 7', 35 cycles of 95° C for 10"/ 60° C for 20" and72° C for 6'. Purified amplicons were amplified again using only the forward primer (0.25 μM) and DTCS dye mix (40%) in a final volume of 10 μL, in 30 cycles of 96° C for 20"/58° C for 20" / 60° C for 3'. Purified sequencing extension products were analyzed on a CEQ-8000 Beckman Coulter genetic analyzer. Sequences were compared with the reference sequence NM_020975.4 and chromatograms were visuallyexamined for mutations using Sequence Investigator software.
Results
The 634 codon mutation was found in 7 patients (17.07%), all of them with MEN2A phenotype. The most frequent was Cys634Arg mutation (5 patients); other variants were Cys634Phe and Cys634Tyr. In one patient with sporadic MTC we found a SNP in codon 649 TCG634TTG with unknown significance. Another SNP, rs1799939 (2071 G/A) was present in 8 MTC cases and 4 healthy screened relatives (without 634 codon mutation).
Conclusion
In our study group RET exon 11 genotyping showed pathogenic mutation of codon 634 in 17.07% patients with MTC, all having MEN2A syndrome. None of sporadic MTC cases presented any pathogenic mutation in exon 11 of RET gene.

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P1201

Serum TSH levels as a predictor of thyroid cancer

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Background
The aim of our study is to show the evaluate relationship between cytological feature of thyroid nodule and TSH level.
Objective
To retrospectively evaluate the usefulness of serum TSH levels as a predictor of thyroid cancer.
Methods
Patients with thyroid nodule(s) who underwent fine-needle aspiration biopsy under ultrasonographic guidance in a Clinica of Administration of the President of the RF were consecutively evaluated.
Results
Eighty patients underwent thyroidectomy and the final diagnoses were malignant in 32(40%) patients, 15 (19%) nodules was follicular adenoma, 33 (41%) was benign nodules. TSH level was significantly higher in patient with thyroid cancer compare with follicular adenoma and other benign nodules.. 30% patients with thyroid cancer had TSH > 2.5 μU/ml and only 18% with follicular adenoma, 12% with other benign nodules had TSH level > 2.5 μU/ml.
Conclusions
Our study showed that patients with thyroid cancer had significantly higher TSH. TSH level is an independent predictor for thyroid malignancy.

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P1202

Impact of pregnancy on follow-up of thyroid papillary carcinoma:- About 30 cases

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Introduction
Thyroid carcinoma is more frequent in women of childbearing age. It can alter both fertility and pregnancy's course.
Objective
The aim of this study was to evaluate pregnancy's influence on thyroid carcinoma's prognosis as a factor of recurrence or progression.
Patients and Methods
We conducted a descriptive cross-sectional study concerning 30 pregnant patients followed for thyroid papillary carcinoma with anterior thyroidectomy at the IBN ROCHD University Hospital of Casablanca's endocrinology department since January 2010. Statistical analysis was univariate for all the variables using SPSS version 22.0.0.
Results
The patients' average age was 35 ± 6.5 years old. Mean duration between first pregnancy and completion of treatment was 4.4 ± 3.1 years. Over an average follow-up period of 2.8 years postpartum, 22 patients were in remission (Thyroglobulin (Tg) < 1 μg /l and absence of morphological abnormality), eight in persistent disease (detectable Tg and / or morphological anomaly). The TSH average rate during pregnancy was 0.83 mIU/l. Cancer progression was correlated with persistence of thyroid cancer before pregnancy ($P = 0.02$) and delayed administration of I-131 therapy ($P = 0.01$). Time between diagnosis and pregnancy, TSH rate during pregnancy, or pre-conception thyroglobulin level did not have a statistically significant impact.
Discussion
Pregnancy's influence on thyroid cancer is controversial. In line with the literature, our study confirms that it has no impact on recurrence or progression of thyroid cancer in patients declared in remission prior to conception.
Conclusion
Only a delay in thyroid cancer's management, in particular, I131-therapy could affect the patients' prognosis undeclared healed during preconception period.

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P1203

Comparative study about differences in staging and prognosis in patients affected or not of BRAF V600E mutation

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Introduction, material and methods
The BRAF isoform of RAF has been implicated in the pathogenesis of papillary thyroid cancer, but not of benign or follicular neoplasms. Also, *BRAF* mutations may confer a worse clinical prognosis than for papillary thyroid cancer without the *BRAF* mutation. Recurrence occurs more frequently when *BRAF* mutations are present. In addition, *BRAF* mutations are associated with extrathyroidal invasion, lymph node metastases, and advanced tumour stage at initial surgery. We have collected the data of our patients with differentiated thyroid cancer during the period from 2000 to 2015. In this study we have mainly compared the frequency of extrathyroidal invasion and lymph node metastases at initial surgery, and recurrences during the follow-up; depending if the patient is affected or not with BRAF V600E mutation. Clinical relevancies have been indicated through prevalence ratio(PR), and statistical differences have been indicated through confidence interval at 95%. Statistical analysis was made with Stata14.
Results
A total amount of 41 valid cases of papillary thyroid cancer were diagnosed during the period from 2000 to 2015. 22 (53.66%) patients were carriers of the BRAF V600E mutation and 19 (46.34%) were not. We compared the patients affected of the mutation with the non-carriers and these were the results: in the case of lymphadenopathies, we have not seen clinically relevant differences (PR 0.87) nor statistically significant (95% CI 0.43 – 1.77). About extrathyroidal invasion, we have not seen clinically relevant differences (PR 0.77) or statistically significant (95% CI 0.27 – 2.24) either. We have not seen either clinically relevant differences (PR 1.22) or statistically significant (95% CI 0.41 – 3.69) in the case of the recurrences. There were not clinically relevant or statistically significant differences in other variables such as multifocality (PR 0.95 (95% CI 0.44 – 2.04)) or the size of the tumour (6.57 mm (95% CI - 0.77 – 13.91)).
Conclusions
In our patients affected by papillary thyroid carcinoma, we have not seen poorer clinical outcomes such as tumour size, lymphadenopathies, extrathyroidal invasion, distant metastasis or mortality. However, the little size of the sample can subtract statistical power from the study. Also, the fact that it is a raw analysis does not allow the adjustment of potential confounding factors that could mitigate the effect.

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P1204

Synchronous thyroid disease in patients with primary hyperparathyroidism

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Introduction
Retrospective analysis has shown that approximately 17–84% of patients suffering from primary hyperparathyroidism have a concomitant thyroid disease. However, it still remains controversial whether these two pathologies happen coincidental or are caused by specific risk factors or genetic changes. In this study we aimed to evaluate concurrently detected thyroid pathologies in patients who underwent surgery for primary hyperparathyroidism.
Methods
We conducted a retrospective study in 75 patients who underwent surgery for primary hyperparathyroidism between 2011 and 2017. Laboratory examination results were recorded and patients underwent preoperative 99 m-technetium sesta-MIBI scan (MIBI) and neck ultrasound (US).
Results
The mean age of participants was 56 ± 12.52 years (Extremes: 28–72) and the sex ratio (Women/Men) was 4.1. Laboratory investigation revealed primary hypothyroidism in 15 patients and hyperthyroidism in three patients. Preoperative thyroid US revealed thyroiditis in four patients (10%), a solitary nodule in 18 patients (24%), multinodular goiter in 18 (24%), and normal findings in 35 cases (47%). Collectively, the prevalence of thyroid disease was 53%. Of 75 parathyroidectomy procedures, 14 patients (18%) underwent simultaneous total or partial thyroidectomy. Indications were suspicious nodule in 11 patients and hyperthyroidism in three patients. Postoperative histopathological examination confirmed the diagnosis of papillary thyroid carcinoma in three patients.
Conclusion
Co-occurrence of thyroid diseases and primary hyperparathyroidism is common. Moreover, coexisting thyroid carcinoma has been reported in patients with PHPT. Although the probability of concomitant thyroid cancer is low, screening for thyroid lesions in patients with primary hyperparathyroidism is recommended. This identification is important prior to parathyroid operation in order to minimize surgical complications, patient discomfort, and costs. Therefore, TSH measurement and preoperative thyroid ultrasound should be performed to patients with primary hyperparathyroidism.

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P1205

Association of thyroid papillary carcinomaand an ectopic parathyroid adenoma

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Introduction
Association between primary hyperparathyroidism and nodular thyroid disease is well recognized, this is mainly due to the high prevalence of this disease. However, association between thyroid carcinoma and primary hyperparathyroidism is less common.
Observation
Fifty-two years old patient with a history of renal colic and upper limb spontaneous fracture was followed for multinodular goiter evolving for 20 years. The patient had clinically diffused bone pain, fatigue and weight loss. Hypercalcemia at 132 mg/l was discovered during pre-anesthetic assessment. The assessment had objectified goiter multinodular classified TIRADS 3, high parathyroid hormone to 256 pg / ml (3 x normal), a right lobar parathyroid adenoma in supraclavicular with thyroid focal area capturing the MIBI scintigraphy. The cervical scan with additional angioscan showed a multi-hetero nodular goiter associated with a nodule above right clavicle inter-aorto-caval measuring 2 cm. The patient had undergone, after medical preparation a total thyroidectomy with resection of the ectopic parathyroid adenoma. Histopathological examination objective a papillary carcinoma with vesicular and insular differentiation and parathyroid adenoma. Evolution was favorable after surgery. The patient presented hypocalcemia needing calcium supplementation orally. Our patient received additional *radioactive iodine* therapy one month after surgery.
Conclusion
The observation of this case emphasizes the importance of a thorough thyroid gland and parathyroid glands evaluation in patients with primary hyperparathyroidism or thyroid disease to reveal or exclude simultaneous presence of a parathyroid adenoma and a thyroid carcinoma.

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ePoster Presentations

Adrenal and Neuroendocrine Tumours

EP1

Is pheochromocytoma a diagnostics chameleon indeed? Series of cases

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Presence of clinical symptoms and signs specific for suspected illness is, in general, a condition *sine qua non* to start diagnostics procedures. However, some diseases may proceed with various and disparate symptoms, which often suggests completely different diagnosis. One of them is pheochromocytoma – rare, usually benign neoplasm derived from chromaffin cells of adrenal medulla. It is very important to diagnose the disease while it is curable by surgery like many tumors but the appropriate premedication is necessary to carry out a successful operation. Unfortunately, the rarity, unspecific symptoms and extremely variable imaging phenotype render the investigation for these tumors very hard. The diagnose of pheochromocytoma is often made too late, and that may be very dangerous for patients. To prove this, we present several patients with completely different course of the disease.
Case 1
'Classic' clinical features (hypertensive paroxysms with tachycardia and sweating) in 48-yr old women with big, high density tumour in left adrenal gland.
Case 2
Paroxysms of sweating and worsening of circulatory insufficiency, without hypertension in 71-yr old women with heterogenic left adrenal mass with signs of bleeding inside.
Case 3
Acute back pain in 50-yr old man with nephrolithiasis and normal blood pressure.
Case 4
Postural hypotension in 62-yr old man with incidentaloma of the right adrenal gland.
Case 5
Panic attacks in 35-yr old woman with 5-cm tumour in right adrenal gland. We analyse clinical sings and symptoms, imaging features (CT, MRI, MIBG), results of biochemical and hormonal investigations of such cases.

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EP2

Gastric NET due to atrophic gastritic combined with multiglandular syndrom type 3

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Introduction
Neuroendocrine tumors (NETs) are neoplasms that arise from cells of the endocrine and nervous systems. They most commonly occur in the intestine and are graded histologically according to markers of cellular proliferation. G1 and G2 neuroendocrine neoplasms are called neuroendocrine tumors (NETs) – formerly called carcinoid tumors. G3 neoplasms are called neuroendocrine carcinomas (NECs).
Objectives
We present a case of a patient with NET G1, type 1 with atrophic gastritis and multiple autoimmune diseases.
Methods
A 75-year-old woman underwent colonoscopy for anemia evaluation. The endoscopic biopsy revealed a low-grade gastric NET G1, 0.9 cm in the body of the stomach, with positive immunohistochemical staining for chromogranin (Cg). Serum gastrin was elevated up to 385 μU/ml (Ref. 28–185) and serum chromoganin-A was 6.1 nmol/l (Ref < 3). The tumor was endoscopically removed.
Results
The patient was also suffering from Hashimoto thyroiditis and hypothyroidism, atrophic gastritis, megaloblastic anemia, vitiligo and rheumatoid arthritis. The biochemical and radiologic evaluation for MEN-1 syndrome was negative. The patient had positive Islet Cell Autoantibodies (ICA) and Glutamic Acid Decarboxylase Autoantibodies (GAD65) and negative antiadrenal antibodies, and she was diagnosed with polyglandular syndrome Type 3 with gastric NET. Three months later the patient underwent a white light endoscopy. The gastric biopsies revealed: atrophic gastritis with intestinal metaplasia and possible microcarcinoids in the body of the stomach. Pathology report revealed linear and nodular hyperplasia of neuroendocrine cells, positive for chromogranin and synaptophysin staining, but not NET. The further follow-up of the patients included regular gastroscopy control and clinical and laboratory evaluation for possible appearance of autoimmune diabetes or adrenal insufficiency.
Conclusions
Patients with atrophic gastritis can develop gastric NET due to hypergastrinemia. Further diagnostic control for autoimmune diseases should be performed for the early detection of a possible multiglandular syndrome, as well as possible autoimmune diabetes and adrenal insufficiency.

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EP3

Neuroendocrine carcinoma of the ampulla of Vater diagnosed preoperatively by endoscopic biopsy

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Background
Neuroendocrine tumors (NETs) of the ampulla of Vater are rare and sometimes difficult to diagnose preoperatively. We report a case of neuroendocrine carcinoma (NEC) of the ampulla of Vater diagnosed by endoscopic biopsy.
Case presentation
The patient was a 83-year-old male complaining of jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) was performed. It revealed a protruding tumor in the major papilla with a diameter of 18mm, and a obstruction of lower bile duct. Endoscopic biopsies from the ulcerative region, and endoscopic retrograde biliary drainege (ERBD) was performed. Pathological findings of the endoscopic biopsies revealed a poorly-differentiated tumor. Immunohistochemically, the biopsied specimens stained positive for chromogranin A, CD56, synaptophysin, and AE1/AE3. The Ki-67-labeling index was 80%. The final preoperative diagnosis was NEC G3. Enhanced abdominal computed tomography (CT) scan revealed a 17 mm slightly enhanced tumor at the ampulla of Vater and some regional lymph node swelling. Pre-operative diagnosis based on CT was difficult since it presented with a similar clinical picture to the adenocarcinomas of this region. Pancreaticoduodenectomy with regional lymph node dissection was performed. Pathological examination revealed a poorly differentiated carcinoma in the region of the major papilla, with a diameter of 20×18 mm. Lymph node on the posterior surface of the pancreatic head (#13) was positive. TNM staging was T2 N1 M0, StageIIb. The immunohistochemical study showed positive for chromogranin A, CD56, Neuron specific enolase (NSE), and synaptophysin. The mitotic index was seven mitoses in ten HPF and Ki-67 was 50%. First-line chemothepapy for the patient might be platinum-based regimens. Because the patient was 83-year-old, postoperative chemotherapy has not performed. Post operative course was uneventful and the patient discharged 24 days after the operation.

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EP4

Diazoxide induced acute renal failure in patient with insulinoma

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A 76-year-old female patient has been admitted to various hospitals with complaints of low blood sugar especially in the morning, sweating, fainting, loss of consciousness, have been suspected of insulinoma with the results of the latest examinations made in 2012, but no focus has been detected. With the same complaints, the patient who applied to our out-patient clinic in December 2017 was subjected to an extended hunger test and invested for further research. Previously, the patient who has HT and COPD diagnoses had a BMI of 39.5 kg/m^2 and no significant physical examination. On the 3rd hour of the prolonged fasting test started at 0800 h in the morning, the blood sugar was 30 mg/dl while the C-peptide was 11.14 ng/ml and insulin was 58.83 μU/ml. Six

millimeter uniformly limited lesion was detected at the head of the pancreas in the withdrawn MRI. The patient was diagnosed insulinoma and EUS was planned, whereas due to technical problems it could not been performed. Triphasic CT was performed instead to clarify the location of the mass and surgical planning. Diazoxide therapy started at the dose of 3×100 mg in the patient who was followed up with Dextroz infusion during this period. After 2 days, the patient's creatine level rose from 1.33 to 2.45, with hypotension, hyponatremia, pretibial +++/+++ edema, and shortness of breath. The patient was evaluated with nephrology and the drug was discontinued due to the development of acute renal insufficiency secondary to diazoxide. The patient was hemodialized for 2 occasional days. Within 3 days, the patient's blood pressure and serum sodium level returned to normal levels. The patient who was followed up with Dextroz infusion was considered to be at high risk for surgery although the biochemical parameters returned to normal. The DOTA-PET was scheduled and until that time 2×1 dose of octreotide 0.1 mg SC short effective treatment was started. The patient recovered from hypoglycemia with this treatment, but sudden increase in creatinine level and atrial fibrillation was observed. We decreased dose of Octreotide to 1×0.1 mg in the patient who started cordarone infusion for arrhythmia. The final creatinine level of the patient was 1.5 and blood sugars were maintained in the normal ranges. The patient was discharged with current treatment to be implemented Radiofrequency occlusion therapy for pancreatic mass. Diazoxide is usually well tolerated whereas could be dangerous simetimes.

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EP5

Isolated pheochromocytoma associated with mutation in the SDHAF2 (SDH5) gene: rare and challenging clinical case

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Introduction
Pheochromocytomas/paragangliomas are rare neuroendocrine tumors. Although mostly sporadic, about 1/3 of the cases correspond to inherited autosomal dominant syndromes, often associated with germline mutations of the SDHD, SDHC and SDHB genes. The association with the SDHAF2(SDH5) gene has been recently discovered, with only few cases published worldwide, and it presents as a paraganglioma of the head and neck, without previous known description of other locations. Its natural history is still unclear, making clinical follow-up truly challenging.
Case report
Forty seven year-old woman, referred to the Endocrinology Department in 2003 by right adrenal nodule of 3 cm, an incidental CT finding. MRI confirmed right suprarenal nodule, well delimited, hypercaptant, with hyperintense signal on T2-weighted-images, that could represent pheochromocytoma. Hormonal study was compatible with non-secretory nodule: metanephrine 96.5 µg/24 h (52–341), normetanephrine 273.1 µg/24 h (88–444), dopamine 234.6 µg/24 h (65–400), adrenaline 2.7 ug/24 h (5–20), noradrenaline 31.7 ug/24 h(15–80), vanillylmandelic acid (VMA) 5.2 mg/24 h (1.4–6.5) and homovanillic acid(HVA) 4.2 mg/24 h(<8.3) in 24-h-urine. The scintigraphy with I131-norcholesterol documented nonfunctioning lesion, aspiration biopsy was suggestive of pheochromocytoma and scintigraphy with I123-MIBG was negative. The patient was proposed to right adrenalectomy, which she declined. She remained under clinical, analytical and imaging surveillance. In the 14-year follow-up with annual CT and MRI, a nodule reduction of 3 cm to 1.7 cm of greater-axis was observed. A PET-FDG and a PET-68Ga-DOTA-NOC were performed in 2012 and were both negative. Analytic control remained without changes. In 2014, the molecular genetics analysis revealed an heterozygotic mutation in the SDHAF2 gene (c.97C>T, p.Arg33Cys), also confirmed in another Genetics Department. At that time, the patient mentioned a cousin living in France probably affected. In 2017, a second review of histological slides maintained the diagnosis of pheochromocytoma. The patient is under surveillance, asymptomatic and without directed therapy.
Conclusion
The authors describe a rare case of isolated pheochromocytoma associated with mutation in the SDHAF2 gene, in a patient who chose not to undergo surgery and represents a true therapeutic and follow-up challenge, given the absence in the literature of case reports with similar clinical presentation and limited knowledge of its long-term evolution. Recent studies suggest that mutation analysis of the SDHAF2 gene is warranted in very young patients with isolated head and neck paraganglioma without mutations in SDHD, SDHC or SDHB genes, and in individuals with family history that are negative for mutations in all other risk genes.

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EP6

Co-existence of malign insulinoma and diabetes mellitus

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Insulinomas are rare neuroendocrine tumors (NETs) of the pancreas with an incidence of four per 1 million persons per year. The co-existence of diabetes mellitus (DM) and insulinoma is very rare. We report a case of 73 year old women with malignant insulinoma and type 2 DM. A 73 year old woman with type 2 diabetes was referred to our clinic for recurrent and severe hypoglycemia especially in the early morning hours. The patient had a history of type 2 DM for 10 years. Although oral antidiabetic drugs are stopped, hypoglycemic episodes persistenly recurred. The patient was hospitalized to investigate the cause of hypoglycemia. At the second day in hospital, the patient experienced a symptomatic hypoglycemic episode. Blood samples taken at that time revealed a low plasma glucose (23 mg/dl) accompanied with elevated insulin and c-peptide levels (17.4 mIU/l, 3,73 ng/l). Cortisol level was 26 µg/dl. Chromoranin A was >500 ng/ml (referange range <94). Calcitonin, parathormon, anterior pituitary hormones and anti insulin antibody test were also in normal range. Abdominal computed tomography (CT) scan showed thickening in the pancreas (14 mm), and multiple hepatic metastatic lesions. Ga-68 DOTATATE PET/CT was performed, which showed positive lesions in liver, pancreas and peripancreatic lymh nodes and also left temporal cortex in brain. Brain CT showed a 15×11 cm nodular lesion in the left temporal lobe with contrast enhancement. The patient refused liver biopsy. The patient was diagnosed as malignant insulinoma.She was discharged on diazoxide 100 mg twice a day and prednisolone 4 mg/day to prevent hypoglycemia. On follow up, diazoxide was stopped due to volume retention and edema. Prednsiolone is stopped due to hyperglycemia and insulin glargine is started together with octreotide LAR 20 mg/month. Three months after the initiation of octreotide LAR injecitons the patient is doing well without hypoglycemia. Diagnosis of malignant insulinoma depends on the presence of metastases.The localization of insulinoma may be difficult.Ga-68 DOTATATE PET/CT is shown to be successfull in localizing insulinomas in clinical studies. The main treatment of insulinoma is surgery if possible. In the present case surgery was not possible due to patients diaspproval. Diazoxide and glucocorticoids are options to prevent hypoglycemia. Somatostatin analogues are effective in controlling hypoglycemia and also have antineoplastic and antiproliferative effects in malignant insulinomas. Insulinoma should be considered in the presence of atypical and recurrent hypoglycemia in patients with diabetes mellitus.

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EP7

An atypical pheochromocytoma presenting with clinical sign and symptoms of non-mechanical bowel obstruction

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Introduction
Pheochromocytomas are rare catecolamin-secreting neoplasms. The classic triad of symptoms in patients with a pheochromocytoma consists of episodic headache, sweating and tachycardia. Gastrointestinal spectrums have been reported such as chronic constipation, intestinal pseudo-obstruction or even intestinal perforation. We describe patient who presented with non-mechanical bowel obstruction and

interestingly hydronephrosis and acute kidney injury as a consequence of an underlying, undiagnosed phaeochromocytoma.
Case report
A-58-year-old man was admitted to the emergency unit with complaints of generalized abdominal pain, constipation and vomiting. The patient had a medical history of hypertension. On initial examination, he had a blood pressure of 180/120 mmHg. He was clinically dehydrated. Abdominal examination confirmed a distended abdomen with reduced bowel sounds. The laboratory investigation results were as follows: creatinine 3.4 mg/dl (0.7–1.1), BUN 127 mg/dl (8.4–25.7). Abdominal radiography showed distended large bowel loops. A CT was arranged and this revealed a unilateral 5 cm right adrenal tumor with bilateral moderate hydroureteronephrosis but no structural cause for the bowel obstruction or hydronephrosis. He required haemodialysis several times because of severe uremia and progressive kidney disease. The patient's serum and 24-hour urine catecholamine levels were high, confirming the diagnosis of phaeochromocytoma. Alpha blockade with doxazosin was administered to control his blood pressure and other symptoms. The hydronephrosis and intestinal pseudo obstruction findings were improved with adequate preoperative alpha blockade. He subsequently underwent uneventful surgical excision of the adrenal tumor. He remained well on follow-up after surgery and the antihypertensive drugs were stopped before discharge.
Discussion
Phaeochromocytoma may clinically manifest as a wide spectrum of gastrointestinal symptoms. The net effect of sympathetic over activity on the α and β-adrenergic receptors is a depressed peristaltic state and constriction of the sphincter, leading to ileus and constipation, as seen in this case. Another interesting feature observed in this patient was the presence of bilateral non-obstructive hydronephrosis. Because of the relaxation effect of the sympathetic system on the bladder and the construction of the internal uretral sphincher, excessive sympathetic stimulation can cause urinary retention and hydroureteronephrosis. This case report draws attention to the patients presenting with adrenal mass and unexplained ileus, constipation and non-obstructive hydroutereronephrosis the diagnosis of a pheochromocytoma should be considered. Our case demonstrates the successful outcome that can be achieved with appropriate medical and surgical intervention, as a delayed diagnosis can cause unfortunate consequences.

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EP8

Malignant and multifocal metastatic pheochromocytoma: a case report

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Pheochromocytoma (PCC) is a rare neuroendocrine tumor, mainly sporadic, many cases are discovered incidentally by computed tomography or magnetic resonance imaging of the abdomen. Malignancy in pheochromocytoma is difficult to diagnose microscopically. Therefore, only the presence of distant metastases, derived from pleomorphic chromaffin cells, is widely accepted as a criterion of malignancy (1)
Case presentation
In March 2016, a 43 year old women presented with an episodic hypertension. Abdomen CT scan showed a mass in adrenal gland measuring 4.2×3.8 cm in the right. Preoperatively blood test confirmed PCC and a right adrenalectomy was performed. After histological evaluation pheochromocytoma was also certified. Patient had remission of symptoms for almost half a year until hypertension episodes appeared again. In September 2017, abdomen CT scan showed a contrast accumulation in the right adrenal place Hormonal test showed a significant increase in chromogranin A level (2594.2 ng/ml), immeasurable plasma normetanephrine level, normal metanephrin (0.2 nmol/l, n. 0–0.456). Other tests (morning cortisol, aldosterone, renin, DHEA-S, 17OHP, PTH levels) were also normal. For further evaluation an I-123 MIBG scan was performed and it showed intensive activity in right adrenal gland projection, moderate uptake of I-123 MIBG in sternum, ileum and low uptake in lowest right costal bone. There were two suspicious activity nodules in the right liver lobe margin, which were confirmed as metastasis during computed tomography imaging of the abdomen and pelvis. During chest CT scan, multiple metastasis in both lungs with pathological mediastinal, parathracheal and axillary lymph nodes were diagnosed. Laparoscopy with adrenal mass and partial liver resection was done. In January, 2018, patient was operated again. Unfortunately, during laparotomy multiple metastases in peritoneum cavity, liver surface, liver gate, ligaments of both small and large intestines were found. Samples from masses in liver gates were taken and malignant PCC was confirmed. At this moment, treatment by chemotherapy is being planned.
Comments
After PCC diagnosis and surgical extirpation, proper, intensive follow-up is very important in case to exlude malignant PCC.
Reference
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EP9

Case report: management of a patient with malignant insulinoma

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Introduction
Malignant insulinoma is a rare functional endocrine tumor of the pancreas. Therefore, there are few data regarding their optimal therapy and long term prognosis. Malignancy is defined by the presence of metastases, mostly in lymph nodes or the liver. Generally these patients present with severe hypoglycemia and require multiple therapies. Here, we described the management of a patient with malignant insulinoma.
Case
A 41-year-old woman with symptomatic and proven hypoglycemia, presented with a 11×10 mm hypodense cystic lesion and a 16×14 mm hyperdense lesion in the tail of the pancreas, and multiple liver metastases following a computerized tomography (CT) scan. Distal pancreatectomy, splenectomy and biopsy from the metastatic liver lesions were performed. Pancreatic resection showed evidence of tumor infiltration into the peripancreatic adipose tissue and extense perineural and lymphovascular invasions. 4 of the 15 resected lymph nodes were evaluated as metastatic. The ki-67 proliferation index of the insulinoma was 7.8%. After surgery, the patient was treated with 120 mg lanreotide autogel/28 days, and with 100 mg of diazoxide two times a day. Dexamethasone therapy was started with 4 mg daily and progressively increased to 16 mg daily. Selective internal radiation therapy with yttrium-90 (Y-90) was administered to treat liver metastases. But the patient did not have benefit from radiation therapy. The patient was evaluated for the liver transplantation because Ga68 scintigraphy showed metastases only in the liver. Although dexthamethasone, lanreotide and diazoxide therapies, hypoglycemic episodes reappeared and she was rehospitalised for persisted hypoglycemia and diuretic resistant edema. Diazoxide was stopped after 6 weeks. Intravenous glucose (10–20% dextrose) infusion and subcutaneous glucagon average 1–2 ampules/day administration were performed. Oral everolimus at a dose of 10 mg/day was also started. Hypoglycemia did not resolve and then parenteral nitrution was performed. Chemotherapy was planned but general status of the patient was deteriorated and patient had respiratory distress due to probably infection or drug associated pneumonitis. Brochoscopy was planned but general status of the patients did not permit the procedure. She died from acute respiratory distress syndrome(ARDS) 3 months after the initial diagnosis.
Conclusion
Refractory hypoglycemia in patients with metastatic insulinoma is an important cause of morbidity and mortality. Surgery is the only curative treatment but does not mostly solve the hypoglycemia caused by malignant insulinomas. For our patient, although hypoglycemic episodes were controlled with aggressive medical treatment, she died due to respiratory distress.

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EP10

A case of oncocytic adrenocortical neoplasm of borderline malignant potencial

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Introduction
Oncocytic adrenocortical neoplasms (OAN) are very rare tumors and they are usually nonfunctional and benign. Approximately 17% of the adrenal

oncocytomas are functional. Their clinical and pathological characteristics are unique. The estimated overall median survival for malignant OANs is more favorable than that of conventional adrenocortical carcinomas.
Case report
We present the case of a 79-year-old male who attended consultations for severe pain in the right side. Among his medical background highlighted high blood pressure and heart failure. Abdominal ultrasound was performed and a solid polylobulated mass was detected in direct contact with the upper pole of the right kidney. Abdominal CT revealed a 9.5×13×12 cm hetegoneous adrenal mass. Overnight low-dose dexamethasone supression test revealed a 0800 h serum cortisol of 0.9 μg/dl. Urinary catecholamines and fractionated metanephrines, plasma testosterone, androstendione and dehydroepiandrosterone levels were within the normal range. Aldosterone and renin levels were compatible with essential hypertension. Adrenalectomy was performed. Histophatological examination described an oncocytic adrenal adenoma. A follow-up thoraco-abdominal scan was performed 6 months after the initial diagnosis and showed a 7 mm lung nodule. Conservative treatment was decided and the TC scan was repeated at 6 months. A 14 mm lung nodule and other smaller pulmonary metastases were discovered. A conservative attitude was decided by the multidisciplinary team due to patient's refusal to receive treatment together with a non-elevated tumor burden and high cardiac toxicity expected from the chemotherapy. OAN are clasified regarding their biological behavior by their histological features according to the Lin-Weiss-Bisceglia system (LBW). The existence of at least one major criterion defines a malignant oncocytoma (>5 mitotic figures per 50 hp fields, atypical mitoses or invasion pf venous structures), the presence of at least one minor criterion defines a borderline oncocytoma, and the absence of all criteria indicates benignancy. In our case, a lesser criterion was met since it was a tumor larger tnah 10 cm.
Conclusions
Commonly OAN of borderline malignant potential seems to have a relatively benign clinical behavior. However, the major clinical problem is to differentiate benign lesions from malignant ones. Further studies are warranted to determine predictors of malignancy and the length, frecuency and parameters needed to follow-up on patients with oncocytic neoplasms of borderline malignant potencial.

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EP11

About a case of an association of two neuroendocrine tumors

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Introduction
Pancreatic neuroendocrine tumors (PNET) are a heterogeneous group with various clinical presentations and lineage. They have an incidence of one per 100 000 individuals per year and represent about 1–2% of all pancreatic tumors. Non functional PNET (NF-PNET) are incidentally discovered in most cases. Pulmonary neuroendocrine tumors constitue a distinct category of tumors with morphologic and biologic neuroendocrine features, they present 20–30% of all NETs and 11–14% of all lung cancers. The association of the two tumors has never been reported.
Case report
We report a case of 46-year old men without particular pathological history admitted to our unit in October 2017 for impairment of general condition and abdominal pain. Clinical examination found a weakened (BMI: 17 kg/m^2) anorexic patient emaciated and jaundice. No carcinoid syndrome or clinical signs of tumor hypersecretion. The thoraco-abdomino-pelvic CT scan objectified a left mediastino-pulmonary mass measuring 162*91 mm with a necrotic pancreatic cephalic mass measuring 34*32 mm. Transthoracic pulmonary biopsy was realized; the pathological study concluded to a large cell lung primitive neuroendocrine carcinoma with positive immuno-histo-chemical study to chromogranin; synaptophysin; TTF1; and a Ki67 very high at 80%. We completed our investigation with a echoendoscopic biopsy of the pancreatic mass. The pathological and immunohistochimical study concluded to a primitive low differentiated pancreatic neuroendocrine carcinoma grade 3 (chromogranine −; synaptophysine +; CD56+; Ki67: 60%). Brain scan has found multiple cerebral secondary locations. Chemotherapy has been proposed to our patient, unfortunately he died before starting this treatment.
Conclusion
The combination of two primitive neuroendocrine tumors at the same time is very rare, the case of our patient is probably the first case reported in the literature.

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EP12

The changing of clinical scenario in three consecutive generations of a Brazilian Family with Von Hippel-Lindau disease

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Background
Von Hippel Lindau Disease (VHL) is an autosomal dominant inherited syndrome characterized by high susceptibility to the development of a wide spectrum of benign and malignant, endocrine and non-endocrine neoplasias in diverse organs of patients harboring a germline mutation in *VHL* tumor suppressor gene. The major clinical manifestations of VHL are brain, cerebellar and spinal cord hemangioblastoma, retinal angioma, pheochromocytoma, renal cell carcinoma and/or cysts and pancreatic neuroendocrine tumor and/or cysts.
Results
From a parental generation whose clinical data are unavailable, two sisters from the 2nd generation (Sibling 1 and Sibling 2) died from brain tumors without pathologic or molecular diagnosis. The first (S1-2ndG) had five children (females =4) and the second (S2-2ndG) had two daughters. From S1-2ndG, 4 siblings were clinically and genetically investigated (3 females; 1 male): two sisters had multifocal pancreatic neuroendocrine tumor and cysts with one of them (S1-3rdG) presenting bilateral pheochromocytoma, while the other (S2-3rdG) had brain hemangioblastoma, endolymphatic sac tumor and retinal angioma. Their brother (S3-3rdG) was diagnosed with retinal angioma and renal cysts, while the 3rd sister (S4-3rdG) was asymptomatic, and negative for the VHL p.Asn78Ser (c.233A>G; exon 1) mutation that was found in all the affected members of this family. From S2-2ndG, one of the two sisters (S5-3rdG) who married with her affected cousin (S3-3rdG) harbored the same mutation found in their cousins and her husband. Exams directed to VHL-related tumors were performed after positive genetic testing, but two at-risk members (S5-3rdG and S6-3rdG) refused molecular diagnosis. From the 4th generation, five at-risk members with ages between 5 and 16 y-old were genetically investigated and all of them were non-*VHL* mutation carriers.
Conclusions
The combined molecular and clinical diagnosis has the potential of reducing VHL-related morbidity/mortality by offering an extensive periodic screening schedule directed to early detection and treatment of tumors in affected VHL patients and asymptomatic *VHL*-positive carriers. In addition, negative-*VHL* carriers are excluded of this preventive program after genetic counseling. Indeed, in these three generations from one VHL family, we could document the natural history of the syndrome in deceased members from the second generation, the impact of clinical diagnosis in the third-generation members and, finally, the benefits of genetic counseling to *VHL*-negative mutation children from the 4th generation.

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EP13

Hypothyroidism occurrence during treatment of neuro endocrine tumor

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Introduction
Several treatments may be proposed against neuroendocrine tumors such as targeted therapies (Tyrosine kinase inhibitors: TKI) and somatostatin agonist. Since the first use of TKI in the oncological field, several studies have shown endocrine side effects type dysthyroidie. Several complex pathophysiological mechanisms and variable from one patient to another have been evoked ranging from a simple thyroiditis to complex autoimmune phenomena (cases of Basedow revealed have been reported as well as hashimoto.
Case
This is a 68-year-old patient cholecystectomized with arterial hypertension and type 2 diabetes who have been on glucophage for 10 years, followed for a

pancreatic neuroendocrine tumor of incidental discovery measuring 54×32 mm, with hepatic metastases. Biological check up reveals chromogranin A < 100 ng/ml. Puted on tyrosine kinase inhibitor 50 miligramms per day, after 3 therapeutic cycles (4weeks ON 2 weeks OFF), acute renal insufficiency appeared (clearance creatinine: 24 ml/min) and hypothyroidism TSH: 40 Uui/ml (0.46–4.6)/ FT4: 9 pmol/l (9.6–31). Treatment with Sinutinib was discontinued due to digestive side effects (grade 4) in addition to hematotoxic effect (Hemoglobin: 8 g/deciliter). Exploration of the cause of hypothyroidism concluded to a destructive cause. Thyroglobulin < 0.2 ng/ml undetectable. Antibodies (Ab) anti tyroperoxidase and Ab Tyroglobulin are normals. Cervical Ultra sound find a normal overall volume of 10 cm^3 with thyroiditis features. The results of histopathological examination of an hepatic metastasis biopsy show proliferation marker Ki67 <3% as well as the digestive intolerance stage 4 have made that Sinutinib is arrested definitively with switch to somatostatin agonists. Hypothyroidism was transient and reversible after 1month stop TKI.

Conclusion

Several studies have appreciated the beneficial effect of hypothyroidism in the survival of renal cancer as well as small-cell lung cancer which is not yet the case To our knowledge for neuroendocrine tumors of the pancreas which will be desirable in the to come up. In the event of confirmation of this latter effect, the treatment of subclinical hypothyroidism (defined by high TSH compared to normal FT4) will depend in this context in the absence of pre-existing cardiovascular pathologies rather than the existence of the symptoms of hypothyroidism. Even somatostatin agonist may have an inhibitory effect on thyroid function which requires regular monitoring of both TSH, FT4 and despite the fact that the mechanism is often central because of the past of destructive thyroiditis in our patient case.

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EP14

Patient harboring RET D631Y mutation with long history of pheochromocytoma without evident medullary thyroid carcinoma

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Purpose

D631Y is a rare mutation associated with MEN2a in which there is an aspartic acid to tyrosine amino acid substitution at codon 631 in exon 11. Common clinical features of this variant of RET mutation are pheochromocytoma in 50%, medullary carcinoma in 30%, primary hyperparathyroidism is very rare. We present the patient harboring RET D631Y mutation.

Clinical case

In April 2017 40-year-old woman was admitted to endocrine department of the Almazov Centre, she presented with paroxysmal hypertension and headaches. She had history of paroxysmal hypertension since age 29. At the age 31 left adrenal pheochromocytoma was revealed and operated on. The diagnosis was confirmed by the pathology. After surgery the blood pressure (BP) normalized. At the age 39 hypertensive crises resumed. In 2017 her blood metanephrine and normetanephrine were elevated: 192.7 pg/ml (0–65), 479.3 pg/ml (0–196) respectively, Chromogranin A level was slightly elevated 127.27 μg/l (0–100), 24-h urinary metanephrines were high: 0.167 μg/day (0–0.04). Abdominal CT demonstrated two right adrenal lesions 1.6×1.5×2.4 sm and 2.7×1.5×2.2 sm. 123I-MIBG scanning showed increased uptake in the right adrenal. Patient's calcitonin level was normal 4.59 pg/ml (0–5), as well as total calcium (2.53 mmol/l (2.15–2.65)), parathyroid hormone (65.21 pg/ml (15–65)). No thyroid nodules were found with the ultrasound examination (US). Right adrenalectomy was done in May 2017. Pathology examination confirmed the pheochromocytoma, immunnohistochemistry staining revealed the STTR2 expression. After surgery BP became normal. In April 2017 genetic testing was recommended, NGS was performed and RET D631Y mutation was found. These results were obtained in December 2017. At that time blood metanephrine was 11.2 pg/ml (0–65), blood normetanephrine was 207.4 pg/ml (0–196), chromogranin A was normal, calcitonin was 8.6 pg/ml (3–19). In January 2018 patient was re-examined: 24-h urine metanephrine level was 0.003 mg/l (0–0.04), total calcium and parathyroid hormone were at normal range. Slight calcitonin elevation was identified: 8.25 pg/ml (<5). Thyroid US revealed a small nodule 0.46×0.37 sm. Pentagastrine was not available, but considering the results of genetic testing total thyroidectomy was recommended to the patient.

Conclusion

Present report supports the relevance of RET testing in patients with pheochromocytoma even if the basal calcitonin over long period of time since the detection of adrenal tumor is normal. Prompt RET mutation diagnosis allows to choose the correct treatment strategy and timely conduct the thyroidectomy.

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EP15

IGF-2-oma: a diagnosis to be considered in a patient with a leiomyosarcoma and recurrent hypoglycemia

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Introduction

Non-islet cell tumor induced hypoglycemia (NICTH) is a paraneoplastic phenomenon involving many types of tumors. It is associated with the secretion of incompletely processed precursors of IGF-2 resulting in a persistent insulin-like activity and hypoglycemia. Most commonly, IGF-2–linked hypoglycemia has been observed in patients with solid mesenchymal or epithelial tumors. Typically, elevated IGF-2 levels are associated with suppressed plasma levels of insulin, IGF-1, and GH. Although the true incidence is unknown, the more recent epidemiologic data suggest that IGF-2-oma tumors are more frequent than previously thought.

Clinical case

A 60-year-old man was admitted in the emergency room with severe asthenia, weigh loss and abdominal pain. Over the last three years he had lost 20 kg in weight. His past medical history was irrelevant. On admission, the physical examination revealed an emaciated patient with a palpable and bulky abdominal mass. Abdominal CT scan showed a very large retroperitoneal tumor, measuring 29.9 cm of greater diameter, with necrotic areas and calcifications of the matrix, occupying virtually the entire abdominal cavity, which histologically proved to be a leiomyosarcoma. Fasting recurrent hypoglycemias associated with neuroglycopenic symptoms were recorded during hospitalization, despite intravenous dextrose. Biochemical investigations revealed: plasma glucose 48 mg/dl with suppressed serum insulin (0.5 μU/ml, normal 2.6–24.9 μU/ml) and C-peptide (0.86 ng/ml, normal 1.1–4.4 ng/ml). Spontaneous hypokalemia was documented (3.2 mmol/l, normal 3.5–5.00 mmol/L). The patient had normal renal and hepatic tests. Thyroid function and serum morning cortisol levels were normal. IGF-1 and IGFBP3 were below normal (8 ng/ml [normal 97–292] and 0.602 mg/dl [normal 3.40–6.90], respectively). β-hydroxybutyrate and IGF-2 levels were not evaluated. The hypothesis of IGF-2-oma was placed and prednisolone 40 mg/day was started with an improvement on glycemic levels. Unfortunately, few days later, the patient suffered from coronary heart failure and died.

Discussion

IGF-2-oma should be considered in unwell patients with very large mesenchymal or epithelial tumors suffering from hypoglycaemic episodes, when insulin and C-peptide levels are suppressed. In our patient, despite the unavailability of high IGF-2 confirmatory levels, GH-dependent proteins IGF-1 and IGFBP-3 reduced levels represent useful additional markers as well as the occurrence of hypokalemia, that is often present and associated with the insulin-like activity of IGF-2.

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EP16

Patient experiences with continouous subcutaneous hydrocortisone infusion (CSHI)

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We recently reported the impact of continous s.c. hydrocortisone infusion (CSHI) on weight, patient AddiQoL scores and healthcare cost savings on five patients. This poster is to follow up on all our patients experiences since started on the CSHI as well as qualitative feedback on the impact on their lives.

This poster also gathered key points on how these patients managed their adrenal crisis.

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EP17

Adrenal ganglioneurosis

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Introduction
Ganglioneuromes are benign tumors from neural crest cells, most often located in the posterior mediastinum and retroperitoneum, and are rarely localized in the adrenal gland. We report the case of a patient.Ho was referred to the incidental alert service
Observation
We report the case of a 45-year-old patient followed by a benign colic sigmoid polypeptide with epigastralgia for which a pelvic abdomino CT scan was requested, demonstrating a left 56 mm adrenal mass. The patient was referred to the incidental alert service. At the anamnesis, it does not report a paroxysmal acute attack, nor weight gain, nor signs of hypercatabolism. A physical examination did not reveal arterial hypertension or signs of hypercorticism, with no milk-spot stain. The hormonal balance had shown normal results, including urinary methoxylates and urinary free cortisol. The patient performed adrenal CT, specifying adrenal mass characteristics, which was hypodense in spontaneous contrast (26UH) moderately elevated after injection of the contrast medium (45UH) with a Wash out at 89%. The patient was operated with left adrenalectomy, with anatomo-pathological study a mature benign ganglioneurome.
Discussion
The diagnostic approach to an adrenal incidentaloma is well codified, determining a precise etiologic orientation, since thorough endocrine exploration and radiological characteristics confirm the accurate diagnosis of certain tumors. Although in certain cases confirmation of diagnosis can only be made by histological examination, as is the case with this patient.

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EP18

Independent ACTH Cushing's syndrome due to unilateral adrenocortical hyperplasia: two cases report

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Introduction
Cushing's syndrome adrenal's origin coul'd be an adenoma, an unilateral carcinoma and rarely a micronodular or macronodular hyperplasia. We report the cases of two patients followed for macronodular adrenal hyperplasia hospitalized in the Ibn Rochd University Hospital, endocrinology department in Casablanca.
Case 1
A 60-year-old patient with independent ACTH Cushing Syndrome with clinical and biological signs of hypercorticism with collapsed ACTH and unilateral adrenal mass at CT. Treatment consisted of an adrenalectomy with a good evolution. The anatomopathological examination objectified a macro-nodular adrenal hyperplasia.
Case 2
A 48-year-old female presented an independent ACTH Cushing Syndrome, discovered with clinical and biological signs, with normal ACTH, and a right adrenal nodule on CT. Patient underwent right-sided adrenalectomy with good progression. Histopathological examination showed macro-nodular adrenal hyperplasia.
Discussion and conclusion
Unilateral adrenal hyperplasia is a rare etiology of ACTH-independent Cushing's syndrome, often taken for adrenal adenoma on CT. This hence the value of histopathological examination for diagnosis confirmation.

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EP19

Adrenal ganglioneuroma: a case report

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Introduction
Ganglioneuromas (GN) are rare benign tumors arising from the neural crest tissue and are most commonly located in the posterior mediastinum and retroperitoneum; they are rarely found in the adrenal gland. We report a case of a female patient with adrenal ganglioneuroma.
Observation
A 51-year-old female patient with no previous comorbidities was admitted to our hospital. She had no significant past medical or surgical history. She had symptoms of hot flush and palpitations since the age of 18. At the age of 34, the patient developed abdominal pain. A physical examination revealed no signs and the results of routine laboratory tests were all found to be within the normal ranges. Our patient underwent computed tomography of his abdomen, which showed a right adrenal tumor. An endocrine workup, including urine catecholamine and a 1mg overnight dexaméthasone suppression test, was normal. The lesion was completely extirpated through laparoscopic resection. The histopathological examination confirmed the lesion as adrenal ganglioneuroma, which contains mature ganglion cells admixed with schwann cells.
Discussion
Adrenal ganglioneuroma is an extremely rare and benign entity comprising schwann cells and ganglion cells. They usually occur in older children and young adults and are the most common sympathetic nervous system tumor in adults. Most GNs are located in the posterior mediastinum and retroperitoneum. TheGN occurs only rarely in the adrenal gland. The clinical presentation of the most patients with adrenal GN is asymptomatic, and most of these tumors are hormone silent as in the present case. Although GNs are generally considered to be non-secretory, some GNs are endocrinologically active. The prognosis for an adrenal GN following surgical resection is good without the need for additional treatment.

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EP20

Malignant sympathetic paraganglioma – case report

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Introduction
Paragangliomas are rare neuroendocrine tumors that arise from the extraadrenal paraganglia. Sympathetic paragangliomas usually secrete catecholamines and are located in the sympathetic paravertebral ganglia of thorax, abdomen and pelvis.
Case report
We present a 66 year old patient with an incidentally found retroperitoneal mass on spine MRI. An open biopsy was performed (9/15) with the histological finding of benign paraganglioma (according to histopathology report from the local pathology). No further controls were provided. In 2017 during MR of the spine (after a sport trauma) progression of the tumor size was found and hormonal evaluation showed significantly increased norepinephrine, normetanephrine and chromogranin levels. Patient presented with paroxysmal hypertension, episodic sweating and tachycardia. ^{18}F-FDG PET/CT showed numerous bone metastatic lesions of spine and ribs. No tumor lesion took up ^{123}I-MIBG and somatostatin receptor scintigraphy is planned to decide if the patient is suitable for peptide receptor radiotherapy or systemic chemotherapy. Due to bone involvement, bisphosphonate therapy was initiated. Results of genetic examination are still pending.
Conclusion
Paragangliomas are rare neuroendocrine tumors. In this particular case, misleading pathological report led to incorrect therapeutic strategy since this tumor type can never be regarded as benign.

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EP21

Bilateral pheochromocytoma in Von Hippel-Lindau syndrome: a case report

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Introduction
Von Hippel–Lindau (VHL) disease is a rare disorder, characterized by the development of a variety of benign and malignant tumors. It is autosomal dominantly inherited disease that causes retinal or central nervous system hemangioblastomas, endolymphatic sac tumors, renal cell carcinomas, pancreatic cysts and tumors, pheochromocytoma and epididymal cystadenomas. The condition is associated with inactivation of a tumor suppression gene.
Case
The 31-year-old Caucasian male patient was consulted in the Hospital of Lithuanian University of Health Sciences, Kaunas clinics ophthalmology department because of the gradually decreasing vision with a right eye. Proliferative retinopathy and retinal hemangioma were diagnosed. VHL syndrome was suspected and abdominal computed tomography (CT) was performed. CT revealed masses in both adrenal glands and MIBG scintigraphy confirmed bilateral pheochromocytoma (PCC). Another diagnostic VHL sign - cysts in pancreas and kidney were also seen in CT. The patient had no clinical symptoms of PCC at that time. To confirm pheochromocytoma, the catecholamine blood test was done and five times elevated normetanephrine 5.65 pmol/l (0–1.037) and chromogranin A 177 μg/l (0–100) were detected. To exclude MEN 2 syndrome genetic test was done and no RET mutations were found. Diagnose of VHL was made based on clinical findings. The multidisciplinary team decided to remove left adrenal gland because the size of the left adrenal tumor was four times larger and in SPECT/CT it had more intensive radionuclide uptake. Histopathological examination revealed pheochromocytoma in 2.4×4×4.3 cm and 3.5×4×2.3 cm size masses with necrotic areas and on immunohistochemistry positive expression of chromogranin A. Catecholamine and chromogranin A levels decreased in one-year follow-up after the operation. Patient lost vision with a right eye because the hemangioblastoma of the retinae was inoperable and complicated in retinal detachment. His family history was unremarkable. Patient was scheduled for follow-up to monitor possible VHL complications.
Conclusion
VHL syndrome is a complex and rare disease, therefore, the diagnosis can be challenging. VHL requires systemic multidisciplinary management to achieve adequate control of these locally aggressive tumors to prevent avoidable morbidity and mortality.

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EP22

Composite pheochromocytoma with neuroblastoma: a case report

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A 24-year old female patient was referred to the endocrinology department after discovery of a left adrenal tumor measuring 4×5 cm, on a CT-scan performed for recurrent back pain. She had a history of lower extremity lymph-oedema since the age of 13 years and juvenile xanthogranulomas operated at the age of 2 years. The tumor had a high density in native CT sequences (48 Hounsfield Units). MRI showed T1 iso-intensity and T2 hyper-intensity, as well as lymph nodes of the celiac trunk. 24-h urine metanephrines were 5 times higher than the upper limit of normal range. I^{123}-MIBG-scan was negative. The patient also fulfilled clinical criteria for type 1 neurofibromatosis (NF-1, Von Recklinghausen disease). After preparation with alpha-adrenergic blockers, a laparoscopic left adrenalectomy was performed. Histology showed composite pheochromocytoma with 30-40% differentiated neuroblastoma, exhibiting a Mib-1 proliferation index of 10-20%. Postoperative plasma-fractionated metanephrines were negative and I^{123}-MIBG-scan as well as PET-CT were normal. Genetic testing did not confirm NF-1 or any other genetic cause of pheochromocytoma. The patient had total thyroidectomy 3 years after initial presentation, for bilateral thyroid nodules with FNA having shown oncocytic follicular neoplasia. Calcitonin levels were negative. Histology only found oncocytic hyperplasia with no proof of malignancy. No tumor recurrence was found at follow-up (7 years). Composite pheochromocytomas are rare tumors consisting of pheochromocytoma and neurogenic tumors (most frequently ganglioneuroma but also ganglioneuroblastoma, neuroblastoma, or peripheral nerve sheath tumor), with only a few series of cases cited in literature. There is uncertainty concerning natural history of these tumors, which often seem to be associated with NF-1. Only a few cases of composite pheochromocytoma with neuroblastoma have been published, and prognosis seems to be related to this latter component. MYC-N gene amplification (negative in our patient) has been found to predict aggressive behavior.

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EP23

Intestinal pseudo-obstruction as a fatal complication of a malignant hereditary paraganglioma: A case report

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Background
Familial paraganglioma type 1 syndrome is a hereditary form of paraganglioma due to an autosomal dominant, paternally inherited, germinal mutation in the SDHD subunit. Intestinal pseudo-obstruction is a rare complication of secretory PGL. We present a case of a patient with a malignant PGL syndrome type 1 who developed intestinal pseudo-obstruction.
Clinical case
The patient was a Dutch male, aged 39 years, carrier of a germinal mutation in exon 3 of the SDHD gene, with multiple malignant and functioning PGLs, with bone, liver and abdominal metastases. In 2007 he was diagnosed with a palpable right cervical paraganglioma that was surgically removed. Noradrenaline was the main secretion product. As disease progressed, multimodality treatment was required: alfa end beta adrenergic receptor blockers, alfa-methyl-p-tirosine, surgically excision of an abdominal PGL, hepatic metastases resection and chemoembolization, radiotherapy for several bone metastases, three Lu177 treatments (total activity $=530$ mCi), decompressive surgery for an orbital bone metastasis, bisphosphonate therapy, and six cycles of cyclophosphamide, vincristine and dacarbazine chemotherapy. Disease progression was evident clinically and biochemically with serum chromogranin A (normal range <100 ng/ml) and urinary metanephrines (normal range <1 ng/ml) reaching 78870 ng/ml and 77 mg/24 h, respectively). By the end of 2017, he developed recurrent vomiting, food intolerance, severe constipation and abdominal bloating. The abdominal CT scan showed massive right colon dilatation without evidence of structural obstruction. Medical therapy with enemas, laxatives, intravenous fluids, erythromycin and neostigmine was started, and phenoxybenzamine dose was increased. However, his condition worsened and a right hemicolectomy with ileostomy was performed, which proved to be ineffective as well. Intravenous phentolamine perfusion and labetalol were then initiated. Unfortunately, due to limited availability of phentolamine and the high dose of continuous intravenous administration that was required, this treatment was unsustainable. Finally, the patient developed gastrointestinal bleeding, dying a few days later.
Conclusion
Intestinal pseudo-obstruction is a severe, rare and often unrecognized consequence of excessive catecholamine production by paraganglioma/pheochromocytoma. Catecholamines activate alfa-1, alfa-2 and beta-2 adrenoreceptors of the intestinal smooth muscle cells, reducing gastrointestinal motility and increasing vasoconstriction. This was a rare case of malignant and secretory PGL with a fatal intestinal pseudo-obstruction complication. Early use of alfa-blockers, in particular intravenous phentolamine, and eventually methyltyrosine, may be useful in relieving this complication which can have a poor outcome.

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EP24

Thyroid nodule and flush syndrome: it's not always a medullary thyroid carcinoma

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Introduction
Neuroendocrine tumors are rare tumors with increasing incidence. They are characterized by the expression of proteins and hormonal products common to neurons and endocrine cells, and are often diagnosed at an advanced stage due to the delayed onset of nonspecific symptoms. We report the case of a patient who presented with a flush syndrome associated with a thyroid nodule and who was subsequently diagnosed with a digestive neuroendocrine tumor

Observation
A 60-year-old patient, chronic smoker, was admitted for a flush syndrome. The interrogation found liquid diarrhea at the rate of 5 stools per day, with palpitations and sweating for 1 year, dysphagia, without dysphonia, or dyspnea, slimming quantified at 14 kg over 15 days, asthenia and anorexia. The examination found a conscious patient, a BMI at 20 kg/m^2, bilateral malar erythema, slightly increased thyroid volume with palpation of a left nodule of 1 cm, slightly sensitive, hard, mobile, without vascular trill, a distended abdomen with hard epigastric mass, hard hepatomegaly, bilateral inguinal lymphadenopathy and edema of the lower limbs. Investigations showed hyperthyroidism with at the cervical ultrasound a multihetero nodular goiter classified TIRADS 3 and a negative calcitonin, thoraco-abdomino-pelvic CT showed duodenal lesion associated with ganglion masses, retractile mesenteritis, hepatic metastases and peritoneal carcinomatosis suggestive of a neuroendocrine tumor. Octreoscan showed a mass of D2 moderately fixing the product with liver metastases.
Discussion
NETs are rare tumors but must be evoked especially in the presence of symptoms indicating paraneoplastic endocrine secretions such as flush syndrome. The most frequent localizations are hailic, then bronchial, colic and gastric. Biologically, the diagnosis is based on the elevation of chromogranin A, blood serotonin and urinary 5-hydroxy-indol-acetic acid (5HIAA). Octreoscan may be useful for the diagnosis and tumor extension assessment. Certain factors favoring the triggering of a carcinoid syndrome are sometimes reported: diet, emotion, anesthesia, alcohol consumption, pentagastrin or catecholamine administration. The factors limiting or suppressing seizures are somatostatin, interferon alpha, antihistamines, alpha blockers, serotonin inhibitors and of course tumor resection.

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EP25

Chemodectoma of carotid glomus coexisting with severe hypercalcemia masking parathyroid gland adenoma – diagnostic difficulties

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Introduction
Chemodectomas of carotid glomus secret mainly catecholamines and/or ACTH. These tumours are very rare cause of ectopic secretion of parathormone (PTH), althought this possibility should be taken into consideration. Therefore, diagnosis of primary hyperparathyroidism (PHPT) as a cause of hypercalcemia in patients with chemodectoma tumours is problematic and may lead to inappropriate diagnosis and treatment. Presented patient is a 64-years old female with non-operative chemodectomas of carotid glomus diagnosed in 1999 with confirmed SDHD mutation. The patient was treated with external beam radiation, and followed-up because of chronic hypercalcemia coexisting with the tumours. In 2010 the patient was hospitalized because of hypercalcemic crisis with serum calcium (Ca) reaching 3.5 mmol/l and PTH values up to 900 pg/ml. The patient required intravenous bisphosphonates administration, which was ineffective. Magnetic resonance (MRI), ultrasound and tomography did not reveal the occurrence of parathyroid adenoma, therefore the diagnosis of ectopic PTH excretion by chemodectoma was formulated. Difficulties in imaging lesions on the neck by ultrasound and MRI may be partially explained by the fact that the patient underwent subtotal thyroidectomy due to nodular goiter in 1987. In 2015 ultrasound examination showed hypoechogenic focal leasion with increased vascularization measuring 18×28×35 mm in the right thyroid bed. Fine needle aspiration suggested presence of parathyroid cells and concentration of PTH in wash-outs of the needle after Fine Needle Aspiration Biopsy (FNAB-PTH washouts) confirmed this suspicion. Patient was qualified to surgery and operated on in December 2015. Histopathological examination confirmed diagnosis of parathyroid adenoma (diameter of 40 mm) and PTH-positive immunohistochemical staining. Chemodectoma tumours are followed-up and show no progression (MRI imaging) and catecholamine/ACTH activity is stable.
Conclusions
Present case is an example of difficulties of PHPT diagnosis masked by coexisting paragangliomas. Suspicion of paraneoplastic syndrome mislead diagnostic process, and as a result imaging concentrated mainly on the radiological follow-up of the chemodectomas.

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EP26

Neuroblastoma in 55-year-old patient - the role of MIBG scintigraphy

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Neuroblastoma is a tumor that originates from immature nerve cells. It is the most common extracranial solid tumor in children, but is extremely rare in adults.
Aim
The role of MIBG scintigraphy in diagnosis and follow-up of patient with neuroblastoma.
Case report
A 55-year-old woman underwent for regular abdomen ultrasound examination. Sonography revealed inhomogeneous, predominantly isoehogenic tumor mass above the upper lobe of the right kidney, measuring 34×45×42 mm. She has been without simptoms. MSCT of abdomen revealed tumor mass in the right adrenal gland that measured 35×45×44 mm. The cathecholamine levels were normal. Laparoscopic right adrenalectomy was done. Pathohistological diagnosis was neuroblastoma. Immunohistochemical profile showed positive chromogranin A, neuron-specific enolase, synaptophysin. Proliferative activity (Ki-67) was 25%. After post-operative recovery scintigraphy with I-131-MIBG and FDG-PET for staging performed and it was negative. MR of abdomen was performed four months and ten months after operation and was negative. Because of neuron-specific enolase elevation, whole body MIBG scintigraphy with SPECT/CT was done. Thyroid blocade with Na-perchlorate had been srarted 30 min before injection of I-131-MIBG and continued during next five days. I-131-MIBG was intravenously applyed in dose of 37 MBq (1 mCi).
Results
Whole body planar scintigrams were performed 24 and 48 hours postinjection and showed intensive focal radiotracer accumulation in the right hemiabdomen. SPECT/CT confirmed accumulation of I-131-MIBG probably in lymph node in the right hemiabdomen, in front of the right crus of diaphragm, at the level of the upper mesenteric artery. The patient underwent extirpation of tumor mass and pathohistology confirmed metastatic neuroblastoma in lymp node.
Conclusion
MIBG scintigraphy with SPECT/CT is very important modality in diagnosis, staging and follow-up of patients with neuroblastoma because it is relatively simple method, with high sensitivity and specificity.

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EP27

Optic neuritis and ectopic Cushing Syndrome: a case report

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Introduction
Ectopic Cushing syndrome caused by a neuroendocrine tumor is uncommon and it's diagnosis is often delayed. Optic neuritis is another rare disease, with some cases also associated to neuroendocrine tumors.
Case-report
A 43-year-old female was referred to the endocrinology outpatient's department due to obesity. She had a past history of bilateral optic neuritis of unknown etiology. She complained of weight gain, hair loss, acne, hirsutism, proximal muscle weakness and visual hallucinations. Physical examination revealed facial plethora, moon facies, supraclavicular fat pads, acne, central obesity, purple striae, ecchymosis, edemas and moderate hypertension. Laboratory evalution showed an elevated ACTH (80–100 pg/ml) and cortisol (20–30 mcg/dL), the latter without a circadian rhythm. Dexamethasone prolonged low and high doses suppression tests showed absent cortisol suppression and the CRH stimulation test did not show an increase in ACTH levels. Pituitary MRI did not reveal any lesion and the inferior petrosal venous sinus catheterization suggested an ectopic origin of the ACTH. A Cushing's syndrome due to an ectopic production of ACTH was admitted, but the imaging study, including chest, abdominal and pelvic CT and MRI scans and an octreotide scintigraphy did not reveal the primitive tumor. The patient was treated with metirapone with non-sustained reduction of cortisol levels nor clinical improvement. Therefore she was submitted to bilateral adrenalectomy, with clinical resolution of Cushing's symptoms and signs, while maintaining raising ACTH levels (189 pg/ml). 14 months after adrenalectomy a new octreotide scintigraphy revealed a right perihilar mediastinic nodular lesion, with a PET scan showing a hypercaptant image at the same location. Nevertheless, the lesion did not appear on the respective CT nor on MRI scans. Tumor marker chromogranin A, started to rise (263 nmol/L), despite a normal

value of 5-Hydroxyindoleacetic acid. A right paramedian pretracheal mass was finally documented on the PET-CT 4 years later. The tumor was removed and the histology revealed a neuroendocrine tumor of lung origin. No recurrence was detected until the present date (55 year-old).
Discussion
Optic neuritis and Cushing syndrome have both been described as paraneoplastic syndromes. However, we haven't found any case described in the literature, combining both syndromes as a result of a neuroendocrine tumor. This case also highlights the long delay that can occur between the paraneoplastic syndromes diagnosis and the neuroendocrine tumor localization.

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EP28

The infradiagnosis of primary aldosteronism as a public health problem

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Objectives
Understanding and propagating the knowledge of the burden caused by the massive infradiagnosis of Primary Aldosteronism (PA), partly due to unawareness of its high prevalence and partly to the complexity of its screening in Primary Care and workup in Specialized Care.
Methods
Review of the relevant literature and personal reflections.
Results
PA is the first cause of secondary hypertension and a highly prevalent disease (2–4%). Of the 16,500,000 Spanish hypertensives, at least 1,000,000 have PA. Norwithstanding, it is still widely considered as a rare disease, with $<1\%$ diagnosed cases; the rest are managed as essential hypertensives. However, PA:
- Is a potentially curable disease, while essential hypertension rarely is.
- Elicits a burden of cardiovascular complications estimated as fivefold that of essential hypertension with comparable blood pressure.
- It has a more severe impact on mental health and quality of life of the patients than essential hypertension, and higher association with metabolic syndrome and sleep-apnea.
- Blood pressure control in PA is not only more difficult (as it typically drives resistant hypertension), but also the risk of cardiovascular events is not reverted unless the aldosteronism is controlled (with normalization of PRA).

The present guidelines recommend screening for PA in multiple situations that may include 50% of the hypertensive patients. Pharmacologic interferences notoriously hinder the interpretation of the aldosterone/renin ratio. Confirmation test are complex, hazardous and may require hospital admission. Subtyping requires in most cases adrenal venous sampling (AVS) which is highly specialized, invasive, costly and poorly standardized. According to the guidelines we should screen about 8,000,000 patients, perform confirmation tests in $>1{,}000{,}000$ and AVS in about 500,000 in order to proceed to resolutive treatment in most of our patients with PA.
Conclusions
PA is not a rare disease, but it is overwhelmingly infradiagnosed, partly because of ignorance and partly because the screening and diagnostic procedures are exceedingly complex and costly. General implementation of the present guidelines is patently inviable, hence it is unsurprising that $<1\%$ of the cases are diagnosed and treated (in Spain as in the rest of the world). Early diagnosis and treatment of PA could potentially reduce very significantly the burden of cardiovascular events (stroke especially) with obvious implications for public health, besides improving the mental health and quality of life of a sizable segment of the population. However, in order to achieve these goals, the PA screening and diagnosis procedures need to be simplified, and their cognizance widened.

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Calcium and Bone

EP29

Patient with post-surgical hypoparathyreoidism and long QT interval

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Post-surgical hypoparathyroidism is most common cause of hypoparathyroidism develops after accidental damage to or removal of the parathyroid glands during surgery. Heart arrhythmias and fainting, even heart failure is reversible complications of hypoparathyroidism, due to low calcium levels. Long QT (LQT) interval may lead to syncope, cardiac arrest, or sudden death. The goal of hypoparathyrodisms treatment is to relieve symptoms and to normalize levels of calcium and phosphorus. A treatment regimen includes: oral calcium carbonate tablets, vitamin D and human parathyroid hormone, recombinant. A treatment of LQT interval with Implantable cardioverter-defibrillator (ICD) is prevention and termination of arrhythmias. Goal is to show a patient with post-surgical hypoparathyroidism, severe hypocalcemia, hyperphosphatemia, hypothyroidism, tetany, syncope and LQT interval.
Materials and methods
A case report of 60 years old woman who has developed post-surgical hypoparathyroidism and hypothyreoidism with the consequence hypocalcemia and prolonged QT interval. Preserved renal function.
Conclusion
Hypoparathyroidism is most commonly caused by surgery. Consequences are hypocalcemia,hyperphosphatemia. In our case is 60 years old patient who is not well-controlled on calcium supplements and active forms of vitamin D (ionized Calcium 0.67 mmol/l, phosphorus 1.59 mmol/l, magnesium 0.79 mmol/l, PTH 0.37 pmol/l) with tetany, syncope, arrhythmia with prolonged QT interval. We perform implantation of cardioverter defibrillator to prevent sudden death. In our country is not available Human parathyroid hormone, recombinant.

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EP30

Evaluation of causes of high parathyroid hormone levels in elderly

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Primary hyperparathyroidism (PHPT) predominantly affects the elderly, with a peak incidence between ages 55 and 70. Parathyroid adenoma is the principal cause, representing 80–85% of all cases. The aim of the study to determine the frequency of parathyroid adenoma in elderly with high parathyroid hormone levels.
Subjects and methods
We performed a retrospective analysis of 31 (30 female, 1 male) elderly wih high parathyroid hormone levels. The demographic caracteristics, biochemical tests and imaging features such as neck ultrasound and parathyroid scintigraphy were evaluated, retrospectively.
Results
The patients had a mean age of 67 ± 8.1 years, serum Ca of 10.9 ± 0.5 mg/dl, serum PTH of 110.6 ± 15.2 pg/ml, serum 25-hydroxy-vitamin D (25- OH D) of 22.9 ± 1.1 nmol/l. Two female patients 2/31) had a parathyroid adenoma shown on a sestamibi scan and neck ultrasound. The frequency of parathyroid adenoma was found to be 6.4%. These patients were underwent *parathyroidectomy* for *primary hyperparathyroidism*. 1 patient presented with severe abdominal pain diagnosed as parathyroid adenoma. Surgery was successful in all patients with no postoperative mortality. 12 patients had low serum 25- OH D (17.3 ± 3.9 nmol/l). Frequency of deficiency of vitamin D was 38.7%. And also, they treated with D vitamin and decreased their PTH levels. No cause was found related hyperparathyroidism with normal 25- OH D using imaging in the rest of them.
Conclusion
High PTH levels due to deficiency of D vitamin levels were higher than parathyroid adenoma in elderly.

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EP31

Interventional study to compare two regimens of vitamin D suplementation

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Introduction
Vitamin D deficiency is very common in our population.It is not clear which is the most effective vitamin D dosing regimen in patients with deficiency.
Objective
To compare two vitamin D supplementation regimen in patients with vitamin D deficiency.
Material and methods
This is an interventional study: Patients atended in our clinic during May and June 2017 with 25-Hydroxyvitamin D below 30 ng/ml were consecutively selected and supplemented with two types of régimen.*Regimen 1*:one weekly calcifediol capsules during a month and then 1 capsule monthly for 2 more months (total 3 months) and *Regimen 2*: 1 weekly hydroferol capsule for one month and then monthly for 5 more months (total 6 months). Each capsule contains 0.266 mg of calcifediol(15.960 IU of vitamin D). In addition, everyone was given dietary advice to increase their vitamin D intake.Half of the patients with levels between 10 and 30 ng/ml were supplemented with regimen 1 and the other half with regimen 2. All patients with levels below 10 ng/ml were given the régimen 2. Vitamin D levels were checked after 6 months.
Results
Data were obtained from 40 patients, mean age 60.7+/−14.5 years(28–86), Mean diagnosis were:47.5% Diabetes/Obesity/dyslipidemia, 35%Thyroid/Pituitary disease,17.5%Malnutrition. Baseline mean 25-Hydroxyvitamin D levels were:15.4+/−4.9(3–23.8) ng/ml and after treatment:33.5+/−13.8 ng/ml(13.4–65,1) ($P<0.05$),with a mean rise of 12.9 ng/ml for patients supplemented with regimen 1 and 21.49 ng/ml for regimen 2($P<0,05$). Baseline deficiency percentage: levels lower than 10 ng/ml, 10–20 and 20–30 ng/ml: 20.5%, 61.5% and 17.9% respectively. After treatment: 10–20, 20–30 and above 30 ng/ml:21.4%,25% and 53.6%. After 6 months 25% of those treated with regimen 1 achieved levels above 30 ng/ml vs the group with regimen 2, which 75% achieved levels higher than 30 ng/ml ($P<0.05$). With régimen 2, only 40% of patients with baseline levels lower than 10 ng/ml achieved 30 ng/ml vs 100% of patients with baseline levels 10–30 ng/ml ($P<0.05$).
Conclusions
In patients with non-severe vitamin D deficiency or insufficiency (10–30 ng/ml) supplementation régimen with 16,000 IU of calcifediol weekly during 1 month and then monthly during 5 months achieve 100% of vitamin D sufficiency (25-Hydroxyvitamin D >30 ng/ml). Patients with severe vitamin D deficiency need other regimens with more doses.

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EP32

Atypical parathyroid adenoma – a rare case of primary hyperparathyroidism

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Introduction
Parathyroid carcinoma and atypical parathyroid adenoma are among rarely encountered causes of primary hyperparathyroidism. Patients with parathyroid carcinoma often differ from those with atypical parathyroid adenoma or parathyromatosis at the time of presentation because patients with parathyroid carcinoma have more profound hypercalcemia as well as invasive tumors. However, at times, it is difficult to distinguish between these conditions both clinically and by final histologic examination.We report the case of a 59 year old woman, who adressed the endocrinology department for assement of macropolinodular goiter with chronic Levothyroxin treatment, polyuria and lombar pain.
Clinical examination
High blood pressure, lombar pain, normal BMD, macronodular goiter, polyuria and polydipsia (about 5l per day).
Lab tests results
Normal CBC, normal fasting plasma gloucose, normal renal function, mild hypercalcemia (12 mg/dl), hyperphosphatemia, normal TSH, high PTH (172 pg/ml), supressed calcitonin; 24h urine sample revealed high urinary calcium, suggesting primary hyperparathyroidism.
Cervical region ultrasound
Macropolinodular goiter, posterior and caudal of the right thyroid lobe a hypoechoic mass lesion (17/9 mm) which seemed to communicate with a blood vessel, resembling a parathyroid adenoma. Lombar spine X-ray: cuneiform compression of L1, narrowing of the intervertebral T12-L1 space. DXA revealed osteoprosis with a increased mineral lost on the distal third radius. Scintigraphy scan of the cervical region was performed with no conclusive findings. The patient was refered to the surgery department for near-total thyroidectomy due to macronodular goiter and to examin and excise what seemed to be a parathyroid adenoma. The histologic examination of the tumor has established the atypical parathyroid adenoma diagnosis. The patient was refered back to us, after three weeks, for the postoperative assessment and she had normal calcemia.
Conclusions
Atypical parathyroid adenoma is a rare cause of primary hyperparathyroidism, no clincal or biological finding can distinguish between the etiological pathways of primary hyperparathyroidism, blood calcium levels do not seem to follow a specific pattern, although, in literature, is mentioned that a higher calcemia is most frequently related with parathyroid carcinoma or parathyroid atypical adenoma. Utlimately the histological exam is the one that clarifies the diagnosis and sets the subsequent therapeutic conduct, so the surgical excision of the suspected tumor is imperative, serving also as therapeutic diagnostic tool.

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EP33

Correlation levels of parathyroid hormone (PTH) and vitamin D (25(OH)D) in different age groups

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Introduction
The general function of vitamin D is to regulate phosphorus-calcium metabolism. Vitamin D takes part in other metabolic processes and it has an impact on body mass and on carbohydrate metabolism. Vitamin D also has an influence on nervous system' functioning and on immune processes. Vitamin D deficiency increases risk of hyperplasia of the parathyroid glands, primary and secondary hyperparathyroidism and osteoporosis.
Objectives
To investigate the reference values of PTH, considering response normalization of vitamin D levels in different age groups.
Methods
The study included 423 patients of both sexes between the age of 18 and 90. The patients were included between September 2017 and November 2017. All patients with endocrine pathology were observed in Moscow outpatient clinics no 5 and no 210. All patients were examined for level 25 (OH) D, PTH, total calcium and creatinine in the blood.
Results
390 patients in the selected age groups had a vitamin D deficiency, which was lower than the reference values. Some of the patients had increased level of PTH. Decreased level of PTH was revealed in all age groups, due to the process of taking saturating doses of the 25(OH)D. Herewith, increased level of PTH was revealed in the age group 60–74 and 75–90.
Conclusion
The results have shown that majority of patients have a pronounced vitamin D deficiency associated with insufficient insolation and malnutrition. PTH level reduction was noticed, due to the process of taking native vitamin D. Respectively, it can be assumed that the reference values for PTH are overestimated in the territory of the Russian Federation, because previous measurements were done without regard to saturation with 25(OH)D.

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EP34

Bone mineral density and polymorphisms of the estrogen receptor gene,vitamin D receptor gene and collagen typei alpha 1 gene

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Objectives
The aim of this study was to analyze the prevalence of some polymorphisms of the CTR-AluI, VDR-FokI, Col1A1y ER-α genes, (involved in bone metabolism),

in our population. And evaluate the association of these polymorphisms with bone mineral density and fracture.
Design, Patients, and Setting
We performed an observational prospective study in pre- and postmenopausal ambulatory women ($n=72$ and $n=152$, respectively).
Intervention
Blood samples were collected at baseline to the measurement of polymorphisms. Women filled out a questionnaire and underwent bone mineral density measurement using dual-energy x-ray absorptiometry at the time of enrollment. We evaluate the incidence of fragility fracture after 1 year of follow-up
Results
The prevalence of the polymorphisms in our population was: *Gen COL1A1SP1*:59% SS, 20% Ss, 21% ss; *Gen CTRALUI*: 5% AA, 41% Aa, 54% aa; *Gen ESR1PPVUII*: 36%PP, 35% Pp, 29% pp; *Gen ESR1XXBAI*: 10%XX, 48% Xx, 42% xx; *Gen VDRBBSMI*: 11% BB 44% Bb, 45% bb; *Gen VDRFFOKI*: 40%FF, 45% Ff, 15% ff. No polymorphisms were associated with low bone mineral density ($P>0.05$). Only an association was found in the postmenopausal group between the polymorphism of the PolESRXX gene and the presence of osteoporotic fracture after menopause ($P=0.02$).
Conclusions
The osteoporosis is a complex and multifactorial disease. Our data don't find any significant association between polymorphisms and bone mineral density. The prevalence of genotyped polymorphisms in our study is consistent with others described in the European population (except for the polymorphism of the COL1A1gene)

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Diabetes, Obesity and Metabolism

EP35

Do our diabetic patients really manage to recognize hypoglycaemia and to act properly in front of it?

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Introduction
Therapeutic education is very important in any patient with a chronic disease such as diabetes. The objective of our study is to evaluate the knowledge of diabetic patients already educated about hypoglycemia.
Materials and methods
This is a prospective study conducted on 50 diabetic patients hospitalized for equilibration of their diabetes in the "C" service of the Tunis National Institute of Nutrition and who were educated beforehand on hypoglycaemia. These patients' knowledge of the defining value of hypoglycaemia and severe hypoglycaemia, signs of hypoglycemia, and their behavior were assessed if they experience hypoglycaemic discomfort.
Results
The mean age of the patients was $68.6+/-11.2$ years. The average body mass index (BMI) was $37.9+/-3.3$ kg/m^2. Diabetes was insulin-dependent in 100% of cases that had been on the move for $16.8+/-8.3$ years on average. Diabetes was poorly balanced in all patients with mean HbA1C of $9.2\%+/-1.1$. Only 30% of patients had a glucometer and regularly monitored their blood glucose. Hypoglycemia was defined by the majority of patients (78%) as having a blood glucose level below 1 g/l. severe hypoglycaemia was defined as glucose lower than 0.5g/L by 86% of patients. The signs of hypoglycemia mentioned by patients are in order of frequency: hunger (100%), palpitations (100%), cold sweats (100%), tremors (96%), neuropsychic disorders (86%) and coma and death (52%) 86% of patients say that clinical signs are a function of the severity of hypoglycaemia.38% only know that if hypoglycaemia recurs, they may not be felt anymore.84% do not know that severe or repeated hypoglycaemia can cause neurologic sequelae. 80% reshape at the slightest malaise without confirming that it is hypoglycemia, even those with a glucometer. They ate bread (37.5%), fruit (30%), a dairy product (25%), chocolate (22.5%) and only 10% re-vegetated properly after confirmation of hypoglycaemia.
Conclusion
The fact of transmitting only information to diabetic patients is not enough to educate them. Therapeutic education must be well structured and patient centered to benefit it.

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EP36

Primary mitochondrial disorders and diabetes mellitus – two case reports

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Introduction
Primary mitochondrial disease is a heterogeneous group of disorders of mitochondrial energy metabolism. Neuromuscular symptoms are the main features, but diabetes mellitus (DM) is present in many patients. DM is related to a deficient energy production, which leads to decreased insulin secretion and ultimately to β-cell apoptosis. In most cases, DM has an insidious onset with requirement of insulin 2-4 years after diagnosis. About 20% of cases present with acute symptoms. We present two cases of patients with mitochondrial disorders, who developed DM.
Case 1
36-year-old male, with mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes syndrome (MELAS) diagnosed at the age of 29, carrier of mtDNA mutation A3243G, with grade 4 tetraparesis, bilateral ptosis, cognitive impairment and epilepsy. He was under carbamazepine, valproic acid, idebenone, mirtazapine, riboflavin and a multivitamin supplement. He was admitted at the emergency department with symptoms of polyuria, polydipsia, dizziness and prostration. Blood tests revealed hyperosmolar hyperglycaemic syndrome, with venous glycaemia 989 mg/dL, plasma osmolality 325 mOsm/Kg, sodium 153 mmol/L, creatinine 1.1 mg/dL, normal pH and negative ketones. He started intravenous insulin and was admitted to the ward. He weighed 40Kg, with BMI 14.8Kg/m^2. Complementary investigation showed A1C 14.9%, C-peptide 0.1 ng/mL (1.0–7.6) and negative islet autoantibodies. He had improvement of clinical status and was discharged home with intensive insulin therapy, with total daily dose of 32U.
Case 2
52-year-old female, with mitochondrial myopathy with Kearns-Sayre phenotype, with grade 4 tetraparesis, bilateral ptosis, external ophthalmoplegia, atrioventricular block (with pacemaker) and chronic respiratory failure. She had past history of papillary thyroid carcinoma (total thyroidectomy at the age of 46), DM diagnosed at the age of 48, hypertension, dyslipidaemia and depression. She was under metformin plus sitagliptin, levothyroxine, telmisartan plus hydrochlorothiazide, bisoprolol, omeprazole, fenofibrate, fluoxetine and valproic acid. She was admitted at Endocrinology department due to uncontrolled diabetes, to start insulin. She weighed 51Kg, with BMI 21.8Kg/m^2. Complementary investigation revealed A1C 10.7%, C-peptide 1.4ng/mL (1.0–7.6) and negative islet autoantibodies. Metformin was suspended due to hyperlactacidaemia and insulin glargine was started. She was discharged home with glargine 18U and sitagliptin 100 mg.
Conclusion
These cases show the heterogeneity of DM in mitochondrial disorders. Differential diagnosis with other forms of DM is challenging, because mitochondrial disorders are rare and present with very different phenotypes. DM treatment at initial stages, before insulin deficiency, is controversial.

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EP37

Features of distribution of fat component in patients with type 2 diabetes mellitus giving insulin

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Background
The central distribution of body fat has been identified as a significant risk factor for development of macrovascular complications in type 2 diabetes mellitus (T2D) in particular. The aim of the study was the features of fat mass distribution in T2D patients using insulin.

Materials and methods
We studied 138 T2D patients with insulin in therapy (31 men and 107 women; mean age 51.43 + 8.41 yrs; disease duration 6.40 + 2.01 yrs; BMI 31.15 ± 1.99 kg/m^2; HbA1c was 8.05 + 0.95%; total daily dose (TDD) of insulin – 0.74 + 0.12 U; duration of insulin using - 3.86 + 0.87 yrs) and 32 matched for age and body mass index controls. The research involved anthropometry, general clinic examination, dual energy X-ray absorptiometry performed on "PRODIGY LUNAR" using program "Total body" and "Body composition".
Results
There were no significant differences in fat component in general group of T2D patients and controls: Total Body 39.10 ± 7.70% vs 36.88 ± 7.84%, $P = 0.057$; Android: 45.35 ± 8.06% vs 44.34 ± 7.15%, $P = 0.393$; A/G Ratio: 1.12 ± 0.19 vs 1.16 ± 0.25, $P < 0.05$; Trunk/Total: 0.58 ± 0.07 vs 0.56 ± 0.07, $P = 0.070$. But in the subgroups of women (T2D vs controls) the following features were established: Total Body 40.75 ± 6.63% vs 41.81 ± 5.34%, $P = 0.384$; Android: 46.38 ± 7.71% vs 46.56 ± 7.28%, $P = 0.898$; Gynoid,%: 43.14 ± 6.95% vs 46.10 ± 5.32%, $P = 0.021$; A/G Ratio: 1.08 ± 0.15 vs 1.02 ± 0.16, $P = 0.033$; Trunk/Total: 0.57 ± 0.07 vs 0.53 ± 0.06, $P = 0.001$; (Arms + Legs)/Total 0.72 ± 0.23 vs 0.87 ± 0.24, $P = 0.001$; Legs/Total: 0.29 ± 0.07 vs 0.33 ± 0.07, $P = 0.001$. Increasing A/G Ratio, Trunk/Total and decreasing (Arms + Legs)/Total, Legs/Total in diabetic patients evidence of fat redistribution in the trunk towards the extremities. Android (central) fat distribution was positively correlated with the age of T2DM women ($r = 0.18$; $P = 0.023$), however no correlation was found with the duration of the disease, level HbA1c, the TDD insulin dose. Similar differences were not found in the subgroups of men (T2D vs controls) in the following parameters: Total Body ($P = 0.271$), Android, % ($P = 0.906$), Gynoid, % ($P = 0.280$), A/GRatio ($P = 0.146$), Trunk/Total ($P = 0.974$), (Arms + Legs)/Total ($P = 0.095$); Legs/Total ($P = 0.976$).
Conclusions
There are differences in the distribution of fat in men of women with type 2 diabetes getting insulin. Women are characterized by a redistribution of fats with an increase in sediment in the trunk region.

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EP38

Hyperglycemia and thyroid disorders in chronic hepatitis C virus infected patients in Fayoum, Egypt

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Background
Hepatitis C virus is common in Egypt and its prevalence varies from 10 to 17%. Beside its harmful effect on the liver, it can lead to variable other effects on various organs and tissues known as the extrahepatic manifestations of HCV. hepatitis C virus induced thyroid diseases in the form of thyroiditis resulting in hypofunction or even hyperfunction of the gland. thyroid disease was found to be of immune nature. Also diabetes which is often termed hepatogenous diabetes was common in patients with chronic HCV and this form of diabetes differs from the classic type 2 diabetes as the patient are usually non obese but have insulin resistance and also the absence of family history of diabetes. interestingly and GAD and anti islet cell antibodies were found in some chronic HCV diabetic patients. The aim of this work is to study the prevalence of hyperglycemia and thyroid disorders in chronic HCV patients.
Patients and methods
This observational cross sectional study included 1400 chronic HCV patients referred to Fayom University hospital, Fayoum general hospital as well as Fayoum insurance hospital for HCV treatment according to the national Egyptian HCV treatment program.
Results
In this study it was found that 90% of the patients had insulin resistance measured by HOMA-IR , 24% had hyperglycemia (16% T2DM, 8% IGT) and 21% had thyroid diseases (hypothyroidism in 13%, hyperthyroidism in 6% and goiter only with normal function in 2% of the studied population)
Conclusion
Hyperglycemia and thyroid diseases are very common in chronic HCV patients and are linked to the extra-hepatic manifestations of HCV

Keywords: HCV, Hyperglycemia, Diabetes, Thyroid, Insulin Resistance
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EP39

The prevalence of risk factors for type 2 diabetes among workers of the industrial enterprisein Minsk with FINDRISK questionnaire

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Introduction
Type 2 diabetes (T2D) and obesity are currently among the most common non-communicable diseases in the world. According to IDF experts in 2015, 415 million people suffered from diabetes, more than 90% of them are in T2D, and half of the disease is hidden and not timely diagnosed.
Aim
To determine risk factors and ten-year T2D risk with FINDRISK questionnare.
Materials and methods
We included 566 people who were proposed to write in FINDRISK questionnaire. We measured height, weight, waist circumference (WC), body mass index (BMI) and blood glucose which was measured by rapid test method. Patients with history of diabetes were excluded. Results are presented as M ± SE, differences were statistically significant at $P < 0.05$.
Results
The study included 310 men aged 48.11 ± 16.35 years, and 256 women aged 48.91 ± 14.53 years. The average age of participants in the action was 44.26 ± 12.62 years, BMI 25.09 ± 3.16 kg/m^2 and blood glucose 5.02 ± 0.42 mmol/l. 46.9% of participants were at low risk for T2D, men (63.7%) were twice as much as women (35.2%) ($P < 0.05$). A low risk of developing CD2 is characteristic of young and middle-aged patients (44.26 ± 12.62 years), height 171.65 ± 8.07 cm, weight 74.19 ± 10.73 kg, with normal or overweight (BMI 25.09 ± 3.16 kg/m^2), WC 83.35 ± 7.89 cm and normal blood glucose 5.02 ± 0.42 mmol/l. 6.2% were registered as patients with high risk, men (44.4%) were a slightly less than women (55.6%). The average age was 55.94 ± 5.61 years, BMI 31,66 ± 2,55 kg/m^2, WC 100,72 ± 8,39 cm, blood glucose 5.43 ± 0.46 mmol/l. According to the results of the study very high risk group of the patients was not identified. In the older age group (over 45 years) the proportion of patients at high risk is significantly more prevalent over the proportion of patients under the age of 45 years with the same risk ($R < 0.001$). Hyperglycemia was detected in 43 participants (7.6%) that was mostly in respondents with increased risk for T2D. During the course of correlation analysis it was found that the age of the respondent ($R = 0.25$), WC ($R = 0.24$), BMI ($R = 0.22$), hyperglycemia anamnesis ($R = 0.21$), arterial hypertension ($R = 0.20$) have the greatest impact on the detection of hyperglycemia.

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EP40

Vitamin D status in a population of type 1 diabetics

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Introduction
Vitamin D deficiency is a health problem related to cardiovascular diseases, autoimmune diseases and cancers. Several studies have shown a significant prevalence of vitamin D deficiency in T1D with positive impact of supplementation on glycemic control. The objective of our work is to evaluate vitamin D status in our T1D patients
Patients and methods
Our study has included 35 patients followed for T1D, vitamin D status was ordered in all patients.
Results
The mean age of patients was 22.5 years, the sex ratio was 1.35 with female predominance. The average duration of diabetes progression was 8.8 years with extremes ranging from 0 to 26 years. The average insulin requirement was 0.85 IU/ kg/day. HbA1C was performed in 54% of our patients and showed poor glycemic control in 88% of cases. Vitamin D levels were within the normal range in 10%, insufficient in 15% and deficient in 75%.
Discussion
Vitamin D deficiency is widely prevalent in T1D, it's able to induce pancreatic islets inflammation inducing an alteration of insulin secretion as well as insulin sensitivity and associated with poor glycemic control. Moreover, it appears that vitamin D has an effect on carbohydrate homeostasis, directly on cell B, and indirectly by regulating calcium levels since insulin secretion is calcium-dependent

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EP41

Diabetic ketosis profile during the month of Ramadan what are the specificities?

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Introduction
Sick or tired subject, just like the diabetic patient, is exempted from fasting during Ramadan, when it can jeopardize health or well being. Nonetheless, many people want to keep holding onto this practice. However, diabetes can be revealed in this context. The aim of the study is to evaluate the characteristics of the diabetic ketosis during this month by comparing them to data far from this period.
Patients et methods
Descriptive, retrospective study about patients hospitalized for diabetic ketosis in endocrinology department of University Hospital, during the holy month of Ramadan 1437 (July 2017), the month before and the one after it. The study concerned 64 patients.
Results
20 diabetic patients hospitalized for ketosis during the month of Ramadan, 21 patients the month before and 23 the one after. The average age of the patients was 43.1 years, with a masculine predominance. The average duration of the diabetes was 5.67 years and 35% of these ketosis were inaugural. Our patients fasted during Ramadan in 76% of the cases. The precipitating factor of the ketosis was infection in 45% of the cases, heart disease in 17%, and an interruption of treatment in 38% of the cases, the insulin deficiency was retained in 12% of the cases. Outside of this holy month, the number of cases of ketosis was not significantly different and the commonest precipitating factor stayed infectious in 40% of the cases.
Discussion
The ketosis during Ramadan is thought to be more frequent. The reasons explaining that are the risk of dehydration, a miss dosing the antidiabetic treatment, and due also to insulin and glucagon alteration. The exempted patients that insist on fasting can put themselves in situations of dangerously severe complications. This severe unbalance concerns, as well, the diabetic patients that are not fasting, because their food habits and lifestyle change during this month.

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EP42

Evaluation of microcirculation in patients with diabetes mellitus by laser doppler fluorometry

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Laser Doppler fluorometry (LDF) is not an invasive method for diagnosing microcirculation in patients with diabetes mellitus, but the method needs to be improved. Evaluation of the LDF method in patients with diabetic neuropathy (DN) before and after the appointment of vitamin D (VD). Included patients with DM and VD deficiency, DM duration more then 5 years, HbA1c up to 9.0%, non-smokers, signed IC. LAKK-M was used. The value of perfusion was measured-M, σ- average modulation of blood flow and CV –coefficient of variation, two functional tests (postural and occlusive). Patients without changing hypoglycemic treatments were randomized into three groups: 5000 IU (group I) and 40 000 IU (group II) per week cholecalciferol treatment and control group (group III). The duration of observation is 24 weeks. Group I included 12 patients (6F) at the age of 56.1 ($\pm$5.4) with an average HbA1c of 8.17$\pm$0.36% and vitamin 25 (OH) D of 21.4$\pm$3.4 nmol/l. Group II included 12 patients (6F), the mean age was 51.3 ($\pm$5.9), HbA1c 8.35$\pm$0.63%, 25 (OH) D 20.9$\pm$4.1 nmol/l. Group III included 14 patients (7F) HbA1c 7.32$\pm$0.19% and 25 (OH) D 27.1$\pm$1.9 nmol/l. The initial parameters of microcirculation did not differ in the three groups (data given in I-II- III groups): M = 10.63$\pm$1.37, 12.36 ($\pm$2.51), 12.36 ($\pm$1.92), σ = 5.32$\pm$0.79, 4.44$\pm$1, 05, 7.1$\pm$0.38, Kv = 11.36$\pm$1.59, 10.64$\pm$2.93, 15.44$\pm$2.49. After 24 weeks HD we found no changes in group I-HbA1c 8.06$\pm$0.39%, 25 (OH) D 24.68 (P = 0.07), M = 10.30$\pm$1.14 (P = 0.08), σ = 4, 98$\pm$0, 56 (P = 0.05) and Kv = 11.82$\pm$2.38 (P = 0.87). Significant differences were found in group II: HbA1c decreased to 7.42$\pm$0.73% (P = 0.023), 25 (OH) D increased to 60.88 (P = 0.003); All parameters were improved microcirculation M = 19.69$\pm$2.52 (P = 0.003), σ = 6.05$\pm$0.93 (P = 0.005), Kv = 13.36$\pm$3.15 (P = 0.017). The indices of group III did not change statistically significant (P = 0.46). The LDF method for the diagnosis of changes in microcirculation DN was informative in conjunction with functional tests. diabetes mellitus; laser dopplerography; Vitamin D

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EP43

Serum levels of vitamin B12 in cobalamin deficient subjects with or without diabetes mellitus

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Vitamin B12 or cobalamin is mainly found in animal origin food products. The frequency of vitamin B12 deficiency varies between 3 and 40% in different populations. Metformin is the first-choice therapy for type 2 diabetics having some side effects, one of them being vitamin B12 malabsorption. The study aimed to evaluate serum levels of vitamin B12 in diabetic and non-diabetic patients with cobalamin deficiency.
Methods
Medical records of subjects having a vitamin B12 level $<$180 pg/ml were screened, consecutive 98 subjects (75 females and 23 males with a mean age of 51.3$\pm$15.9 years) were included in the retrospective study. 34 had the diagnosis of type 2 diabetes mellitus. Mean fasting blood glucose level of the diabetics was 128.1$\pm$8.3 mg/dl and mean HbA1c was 6.3$\pm$0.2%. Thirty DM patients were using metformin treatment in a dosage of 2 g/day.
Results
The mean age was 59.0$\pm$10.8 years in diabetics and 47.2$\pm$16.8 years in nondiabetics. Mean BMI was 27.8$\pm$6.2 kg/m^2 and mean vitamin B12 level was 139.3$\pm$29.2 pg/ml for whole population. Mean vitamin B12 level was found to be low in diabetics compared to nondiabetics (131.2$\pm$30.6 and 143.5$\pm$27.7 pg/ml, respectively, P = 0.05). There were accompanying illnesses other than DM in whole group. Thyroid abnormalities without autoimmunity including multinodular goiter were present in 22 patients, dyslipidemia in 16, Hashimoto thyroiditis in 16, hypertension in 10, hirsutism in 5, hyperprolactinemia in 5, gastric problems in four, chronic kidney disease in three, panhypopituitarism in three, osteoporosis in two, heart failure in two, parathyroid adenoma in two, stomach cancer in one and lung cancer in one patient. Among comorbidities, as being autoimmune, Hashimoto thyroiditis can be together with insufficient absorbtion of vitamin B12. In the group with DM only three had accompanying Hashimoto thyroiditis. Vitamin B12 levels of subjects with Hashimoto thyroiditis did not differ those of subjects without Hashimoto thyroiditis (142.6$\pm$32.5 vs. 138.6$\pm$28.7 pg/ml, respectively).
Conclusion
Our results demonstrated that vitamin B12 levels were similar in diabetic and non-diabetic subjects with cobalamin deficiency. All patients with or without the diagnosis of diabetes should be encouraged for sufficient vitamin B12 intake and all possible factors that lead to deficiency should be eliminated.

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EP44

Are plasmathyrotropin levels associated with degree of obesity and metabolic syndrome in euthyroid obese patients?

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We aimed to observe the association between degree of obesity and metabolic syndrome and plasma thyrotropin levels in obese, euthyroid patients. 947 obese and overweight patients who admitted to our outpatient clinic were assessed retrospectively. 150 healthy euthyroid cases were also recruited as the control group. Cases with metabolic syndrome were determined. Patients were divided into various subgroups as overweight, obese, morbid obese, men, and women. No statistical significance was determined when all the patients' and subgroups' plasma thyrotropin levels were compared to normal weight control group. No association was shown between the presence of metabolic syndrome and plasma thyrotropin levels for both all patients and subgroups. Also there was not any association between each component of metabolic syndrome and plasma thyrotropin levels. In conclusion, we did not found any significant association between plasma thyrotropin levels and obesity and metabolic syndrome in our euthyroid-obese cohort.

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EP45

The efficacy of glp-1 analogue therapy in patient with hypotalamic obesity

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Craniopharyngiomas are rare tumors that in a high percentage of patients leads to damage of periventricular nucleus and suprachiasmatic nucleus, what leads to the development of hypothalamic obesity. Hypotalamic obesity is associated with numerous metabolic disorders. Regardless of the numerous studies of new therapeutic approaches, there is still no official approved effective (phramacological or bariatric) treatment for hypotalamic obesity. Liraglutide is an GLP-1 analogue that stimulates insulin released from beta cells of pancreas after eating, suppresses glucagon secretion and induce the weight loss. It is proposed that liraglutide has the peripheral and central effects in the maintenance of weight loss, but the clear mechanism of liraglutide action in CNS is still lacking. We present the case of patient who was diagnosed with craniopharyngioma as a 31 year old after sudden headache attack, followed by vomiting and unconsciousness. CT scan showed an expansive, suprasellar cystic tumor of dimension 25×27X21 mm with pituitary compression. Three years before diagnose of head tumor, the patient had a markedly enhanced appetite, causing the significant weight gain (>20 kg), and consequently the diagnose of arterial hypertension, hyperlipoproteinemia and type 2 diabetes. After the operation of the tumor was performed (PH: Craniopharyngeoma papillare, WHO grade I), endocrinological testing showed panhypopyuitarism and uncontroled diabetes (HbA1c 10.3%) with obesity (BMI 31.9 kg/m^2). Replacement therapy with hydrorortisone, levothyroxine and testosterone were induced, but also the liraglutide as an antidiabetic drug. Three months later, the patient was well hormone substituted and has the better glycemic control (HbA1c 8.2%). Also, he lost 5 kilograms. Continuous loss of the weigt was obsserved 6 months. The plato was achieved on BMI 26.8 kg/m^2 by maximally tolerable dose of 1.2 mg/day of liraglutide, with well-control diabetes (HbA1c 7.3%). Further researches and results of randomized studies are needed in order to prove the efficacy of GLP-1 analogues as therapy for hypothalamic obesity.

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EP46

Relation between eating behaviors, exercise and weight loss in post bariatric period

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We analyzed the eating behavior and physical activity in patients operated in our obesity surgery center and their relation to weight loss. We mailed to patients a simple self-questionnaire to assess the use of eating or physical activity advices given from our stuff during the preoperative period. Patients had a bariatric surgery from September 1, 2013 to August 2016 Questionnaires were collected during their follow-up (September 2017). One hundred forty four out of 750 patients answered this questionnaire. The mean age was 45 ± 10.48 years, 81% were women, the average BMI before intervention was 45.03 ± 7.1 kg/m^2 and 133 had longitudinal sleeve gastrectomy. The mean BMI loss was 13.92 kg/m^2 and the average follow-up 2.07 years. Analysis of the questionnaires revealed that 64% of patients had physical activity that lasted less than 30 min/day Among patients 46% declared abnormal hungriness, 60% completed their meal in less than 20 min, 18.7% had regular chewing gum consumption, 32% had more than three snacks a week in, 66% had sugar consumption more than twice a week in, and 18% had less than three meals a day Female sex and a meal duration <20 min and meal duration <20 min were significantly related to lower BMI loss (13.4 vs 15.8 kg/m^2, $P=0.0049$; 13.6 vs 14.4 kg/m^2, $P=0.0002$; 12.2 vs 14.3 kg/m^2, $P=0.0307$; respectively). Fast eating was related to a lower weight loss in bariatric surgery patients.

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EP47

Weight loss 6 months after sleeve gastrectomy

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Aim
The aim of our study was to evaluate the impact of sleeve gastectomy on weight loss 6 months after surgery.
Methodology
This was a prospective study including 30 obese patients undergoing sleeve gastrectomy. Their weight,height, BMI, fat mass index and waist circumfernce, were measured at baseline and 6 months after surgery.
Results
Mean patient age was 36.77 ± 7.82 .80% of the study patients were women. There were significant changes in all anthropometric measurments before and after surgery. Average excess weight and average excess BMI lost at 6 months were respectively 43.53 and 50.37%.There was a significant association between excess weight lost and respectively age,preoperative BMI,preoperative fat mass index and preopeartive waist circumfence.
Conclusion
Our data suggest that sleeve gastrectomy is an effective procedure in morbidly obese patients that leads to an important weight loss.

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EP48

Diabetes during paraneoplastic cushing: about two cases

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Diabetes in paraneoplastic Cushing is often severe with a risk of acute metabolic complications.
Observation n° 1
A 36-year-old patient, with no medical history, was hospitalized for inaugural diabetic ketoacidosis with no intercurrent infection. The physical examination found facio-truncal obesity, amyotrophy of extremities, melanoderma, arterial hypertension and severe psychiatric disorders. The blood tests showed an hypokalemia at 1.9 mmol/l. High doses of insulin were required to control the diabetes. The diagnosis of an ACTH-dependent Cushing Syndrome was retained in the presence of high cortisol levels (2000 nmol/l), non-suppressed after dexamethasone suppression test (DST), and high ACTH levels at 466 pg/l. Conventional localization techniques (Hypothalamic-pituitary MRI, cervico-thoraco-abdominopelvic CT, bronchial fibroscopy, octreoscan scintigraphy) failed to show any tumor. Bilateral adrenalectomy (in two phases) was performed because of the severity of the patient's condition with no obvious etiology. The clinical course was marked by an improvement of the clinical signs and even a diabetes remission (we stopped all antidiabetic drugs). Two years later, Cushing syndrome recurred with the reappearance of diabetes requiring an insulin therapy. Cervicothoracic CT showed a right anterior mediastinal nodule and it was octreoscan-positive. The patient had a total thymectomy. Histology confirmed an atypical carcinoid stage III thymos tumor. The patient underwent radiotheray. The Cushing syndrome disappeared and the diabetes was well balanced under low metformin dose.
Observation n°2:
A 35-year-old patient with no medical history, smoking 35 pack-year, was hospitalized for inaugural diabetic ketoacidosis requiring intensive insulin therapy. The physical examination found a patient with debilitating medical conditions, facio-truncal obesity and melanoderma. The blood tests showed an hypokalemia. The diagnosis of ACTH-dependent Cushing was retained in the presence of hypercorticism (cortisol = 2900 nmol/l), non-suppressed after DST, and high ACTH levels (980 µg/l). This was a paraneoplastic cushing due to pulmonary neoplasia identified on chest X-ray and thoracic CT. The diabetes remained very unbalanced (Glycemia at 30 mmol/l) despite high doses of insulin (>0.5 IU/kg per day). The evolution was quickly fatal. The patient died of acute respiratory failure during bronchial fibroscopy.
Conclusion
These two cases clearly show that secondary diabetes can be very severe and difficult to balance based on the severity of the underlying endocrinopathy.

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EP49

Diabetes profile during cyclic Cushing syndrome: about one case

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Endogenous Cushing's syndrome comes generally with permanent hypercorticism often complicated by diabetes which can be difficult to control. However, the cortisol's excessive production may be cyclic or intermittent, and, therefore, complications may have a specific course which leads to diagnostic and therapeutic delay.
Observation
We report the case of a 28-year-old woman with no previous medical history who was hospitalized for a Cushing's syndrome. The clinical picture was marked by severe hypertension requiring triple therapy and poorly-controlled diabetes under intensified insulin therapy (0.7 IU/kg per day). Cushing disease was diagnosed in the presence of high cortisol levels (800 nmol/l), not suppressed after dexamethasone suppression test, and high ACTH levels (106 μg/ml). Surgery was not indicated since the pituitary MRI was normal but the evolution was spontaneously favorable. The clinical signs of Cushing syndrome regressed, blood pressure levels got back to normal and diabetes was cured (we stopped all diabetes medications) for eight years, then Cushing syndrome recurred. The diabetes reappeared requiring once again high doses of insulin (0.9 IU/kg per day). The hormonal assessment was in favor of Cushing disease and the pituitary MRI did not show any abnormalities. Once again, the patient went spontaneously into remission. Blood glucose levels were well-controlled only by metformin. Four years later, Cushing's syndrome recurred a second time. Diabetes reappeared requiring intensive insulin therapy (0.6 IU/kg per day). Pituitary MRI showed a microadenoma. The patient underwent surgery with complete remission of the Cushing' syndrome and was cured from her Diabetes.
Conclusion
This case highlights the hyperglycemic hormones role in the genesis of diabetes through its cyclic evolution during a cyclic Cushing.

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EP50

Diabetes mellitus development secondary to chronic pancreatitis in a kidney transplant recipient

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Acute pancreatitis in kidney transplant recipients is an infrequent complication with complex etiology. However, there was no enough data about chronic pancreatitis after kidney transplantation. Glucose intolerance occurs with some frequency in chronic pancreatitis, but overt diabetes mellitus usually occurs late in the course of the disease. We presented long-term course of a kidney transplant recipient who developed recurrent acute pancreatitis.
Case report
A 43-year-old female patient underwent cholecystectomy due to pancreatitis attack secondary to cholelithiasis on January 2008. She had no history of obesity, dyslipidemia, diabetes and alcohol abuse. She received a successful kidney transplant from a deceased donor in our center on March 2008 because of end-stage kidney disease. Post-transplant immunosuppressive treatment consisted of prednisolone, mycophenolate sodium and everolimus. Gemfibrozil was started 600 mg daily due to her high serum triglyceride level (592 mg/dl) on May 2008. After a week, she was admitted to the emergency service because of abdominal pain, nausea, vomiting, mild dehydration and upper abdominal tenderness. Her tests revealed a serum glucose of 120 mg/dl, total cholesterol 306 mg/dl, triglyceride 323 mg/dl and amylase 746 IU/l. Acute pancreatitis complicated by a pseudocyst was diagnosed and treated. Hyperglycemia that developed during this period was treated with insulin administration. Fenofibrate and pravastatin were started. After sphincterotomy to pancreatic duct and a biliary stent insertion by ERCP, her complaints resolved. Then, the pancreatic biliary stent was removed. In 2009 and 2016, acute pancreatitis recurred due to stones. The head and corpus of pancreas were atrophic. Pancreatic duct was enlarged. In 2013, a 2-h oral glucose tolerance test was performed due to hyperglycemia (fasting glucose 129 mg/dL and 2nd hour glucose 178 mg/dl, HbA1c 6.5%). The patient was started insulin glargin treatment (10 U/d) with a diagnosis of secondary diabetes mellitus. Then, metformin (2×500 mg) was added to the treatment. She went on her follow-ups with a serum creatinine of 0.8 mg/dl (glucose; fasting: 89 mg/dl, postprandial: 108 mg/dl, HbA1c 6.2%, total cholesterol 211 mg/dl, HDL cholesterol 65 mg/dl, LDL cholesterol 110 mg/dl and triglyceride 176 mg/dl) with medical treatment.
Conclusion
Chronic pancreatitis is an inflammatory condition. The clinical manifestations of this disorder include chronic abdominal pain and pancreatic exocrine and endocrine dysfunction leading to secondary diabetes. When needed, these patients should be treated with insulin and oral hypoglycaemic agents.

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EP51

Familial chylomicronemia with multiple complications

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Background
Familial chylomicronemia is a rare disorder of lipoprotein metabolism characterized by severe fasting hypertriglyceridemia. We present here a case of severe familial chylomicronemia with multiple complications.
Case presentation
A 35-year-old Tunisian woman was suffering from chylomicronemia (Fredrickson type I hyperlipoproteinemia) since the age of 10 years old. Her dyslipidemia was caused by a lipoprotein lipase deficiency. Since her childhood, she was instructed to adhere to a low fat diet with prescription of omega-3-fatty acids. Her diet was sometimes enriched with medium chain triglycerides (MCT). However, her adherence was unsatisfying. Her last laboratory examination revealed a milky blood sample, marked elevation of Triglyceride (41.29 mmol/l), of cholesterol (91 mmol/l) and of gamma-glutamyl transferase (11*normal) whereas hemoglobin was remained low at 8 g/dl. Her liver transaminases, alkaline phosphatase, lactate dehydrogenase and amylase were normal. Her past medical history revealed recurrent bouts of pancreatitis since she was 25 years old. All the episodes of acute pancreatitis were associated with major hypertriglyceridemia. There was a history of eight episodes of acute pancreatitis with the development of severe local complications. Two pancreatic pseudocycts were formed. The patient had undergone a gastro-entero-anastomosis for the biliary-digestive compressive syndrome caused by pancreatic pseudocycts. Further hospital admissions occurred because of gastro-esophageal variceal bleeding. Indeed, pancreatic pseudocycts were complicated by regional portal hypertension that gave rise to gastric and oesophageal varices. The patient was kept under beta-blocker (propranolol) treatment. Endoscopic injection of biological glue was performed. For her, it required 17 sessions. Her first pregnancy was interrupted because of the occurrence of acute pancreatitis at the 24th week of pregnancy. Fortunately, thanks to good adherence to low fat diet, her chylomicronemia was successfully managed during her second pregnancy and a healthy preterm infant was born at 35 weeks of gestation.
Conclusion
In conclusion, this case shows the large number of complications that may cause familial chylomicronemia. The ffective management of hypertriglyceridemia would potentially decrease the occurerence of complications. Hence, health providers in should underscore the benefits of continuing and adhering to the low fat diet.

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EP52

Association of hyperlipidemia with cancer colon

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A 46-year old male patient, living in Giza, father of 4, used to work as a baker. He is an ex-smoker. He has diabetes on insulin for 4 years, not hypertensive.He was diagnosed to have colonic carcinoma upon which surgical intervention was done in the form of right hemicolectomy with splenectomy and cholecystectomy. Postoperative pathology report revealed invasive moderately differentiated adenocarcinoma. He received postoperative chemotherapy, twelve sessions over the past one and half years. During the treatment he developed recurrent attacks of pancreatitis and was discovered to have hyperlipidaemia upon which four sessions of plasmapharesis were done and the patient was discharged on statins and fibrates. One of his brothers has diabetes and cancer colon, the other brother has colonic polyps. His uncle and two of his cousins died from cancer

colon. There is positive consanguinity. There is a family history of ischemic heart disease.
Examination
The patient is cachectic, BMI: 19.5 kg/m^2, Blood Pressure: 110/70. Pulse: 100 BPM regular, Temp: 37.2–37.6 °C, RR: 16/min. Head and neck examination showed wasted masseter & temporalis with prominent zygoma. Fundus examination was normal. Abdominal examination showed mid line scar 25 cm healed by secondary intension, appendectomy scar healed by secondary intension, no organomegaly. Chest, cardiac and neurological examination were free.
Investigations
CBC, kidney and liver functions, serum amylase and lipase were in the normal range. HbA1c: 13.74%, (4–5%), total cholesterol: 870 (200 mg/dl),triglycerides: 9527(150 mg/dl),HDL: 227 (60 mg/dl),LDL: 57 (160 mg/dl). Echocardiography showed grade I diastolic function. Contrast CT abdomen and pelvis showed no focal lesions or dilated IHBRs, normal CT appearance of the pancreas, spleen, aorta, IVC and both kidneys. No areas of abnormal pelvic enhancement or collections. No pathalogical enlarged LNs, no ascites.
Conclusion
Our patient had familial adenomatous polyposis (FAP) which is characterized by the development of hundreds to thousands of colonic adenoma, it usually leads to inevitable colorectal carcinoma in untreated individuals. FAP are caused by germline mutations in Adenomatous Polyposis Coli (*APC*), which encodes a tumor suppressor that is part of the WNT signaling pathway. The link between germline mutations and APC FAB & hyperlipidemia that it was found experimentally, that mice with mutation of APC gene show decreased adipogenesis but paradoxically elevated serum lipid level. It is caused by downregulated expression of FFA use genes in white adipose tissue (WAT) of old mice.

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EP53

Vascular surgeons: do they ask enough?

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Introduction
Consultations are a common practice among different units of a hospital. In particular, those from the Vascular Surgery Service (VS) to the medical units are some of the most frequent.
Objectives
Analyze the total number of consultations performed from the Vascular Surgery Service (VS) service to a medical team (T) specifically assigned to the control of decompensated medical conditions in surgical areas, in relation to the number of total admissions in that area.
Material and methods
Descriptive analysis on the total number of consultations sent quarterly from VS to T. It is compared to the total number of VS admissions.
Results
From January 2011 to November 2014 173 consultations were sent from VS to T. The total number of consultations progressively increased in time. There was a very significant decrease in the 3rd quarter of 2013, due to the assignment of VS admitted patients to a new professional who was not informed of the existence of T, sending 2 consultations during the trimester. These figures were compared with the total number of VS admissions during the same period. The number of admissions remained approximately constant throughout the period, with the lowest numbers declining in the third quarter of each year, coinciding with the summer holiday period. In the first year of T activity, the% of patients consulted is slightly higher than 6%. Subsequently stabilizes around 10% (except for the aforementioned 3rd trimester of 2013) of hospitalized patients. In 2014 the percentage decreases to 7.36%.
Conclusions
There is an increased demand for the assessment of patients admitted by VS to Internal Medicine, Nephrology, Penumology, Endocrinology and Cardiology in the first year of T. Although this demand tends to stabilize later around 10%, in the last year it decreases, probably due to the interest shown by VS professionals in improving the control of the medical decompensations of their patients. This did not correspond to a higher or lower number of VS admissions. Taking into account the great comorbidity and vascular risk factors of VS patients, the data suggest a good control of the medical decompensations by VS professionals.

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EP54

Diabetes and other frequent clinical problems in patients admitted in vascular surgery

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Objectives
To analyze the most frequent consultations on patients admitted to VS sent to a medical team (T).
Material and methods
Descriptive analysis of consultations on patients admitted to the VS who suffered any medical decompensation that needed to be notified to Internal Medicine, Cardiology, Endocrinology, Nephrology or Pneumology.
Results
From February 2011 to November 2014, 173 consultations were sent from the VS Service to T. The most common consultation was 'dyspnea' in 62 (35.8%), followed by "pluripathology control" in 18 (10.4%), "decreased level of consciousness" in 13 (7.5%), 'fever' in 13 (7.5%), 'renal failure' in 7 (4%) and "blood pressure control" in 7 (4%) patients. The reason for the consultation was 'poorly controlled DM' in 8 patients (4.6%) of whom had hyperglycemia 4 (50%) and hypoglycemia, 4 (50%) as well as "control of vascular risk factors" in 18 (10.4%). However, after analysis of all patients, only 22 (12.7%) were diagnosed as decompensated DM in the discharge report.This implies a real decompensation of 23.4% of patients with known DM.
Conclusions
More than one third of the consultations for medical decompensations in the patients admitted to the VS unit correspond to dyspnea. DM is a single cause of medical decompensation in 4.6% of patients admitted to VS. However, associated with decompensation of other vascular risk factors, one out of four known diabetics had abnormal blood glucose levels. We suggest that an early evaluation of all these processes that could induce to heart failure, blood glucose and blood pressure performed by Cardiology, Endocrinology or Internal Medicine could be beneficial in terms of morbidity and hospital stay, since previous studies associate the diabetic uncontrolled in patients admitted to Vascular Surgery to an average stay 9 days superior compared to non-diabetics.

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EP55

The risk of symptomatic hypoglycemia over 4 years of intensive insulin treatment and combined therapy in type 2 diabetes patients

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The aim
To evaluate the risk factors for symptomatic hypoglycemia (SG) over 4 years of intensive insulin treatment (IIT) and combined therapy (CT) in type 2 diabetes.
Material and methods
Under our supervision in the departments of the Center of Endocrinology of PH Ministry of RUz in the period from September 2016 for December, to 2017, 20 patients were observed with DM 2, men – 9, women – 11; 54.5 ± 1.5 m/61.6 ± 1.8 w years old. The remoteness of disease hesitated in limits from 7 to 9 years. All patients were observed by standard rules.
Results
Patients were distributed on two groups: 1 gr – 10 patients (5/5), which received IIT, 2 gr – 10 patients (4/6) on CT (insulin + Metformin, SM, etc). In 1st gr BMI 28.5 ± 1.5/27.14 ± 1.8, in 2 gr – BMI 36.6 ± 1.4/31.6 ± 1.2. For patients with DM 2 on IIT we found the duration of IIT – more than 3.6 years for men and 5 years for women. In second group the start of IIT – more than 3.75 years for men and 5.1 years for women. The middle range of HbA1C in 1st gr: 7.3 ± 0.2 for men and 7.9 ± 0.4 for women. The middle range of HbA1C in 2nd gr: 8.4 ± 0.4 for men and 8.02 ± 0.5 for women. Among comprehensive diseases we found in 1st gr: ischemic heart disease (IHD) 1/3, arterial hypertension (AH) 5/5, dislipidemiya (D) 0/1, liver cirrhosis 1/0, diabetic nephropathy (DN) II-III 5/2. In 2nd gr: IHD 0/4, AH 4/4, D 1/0, DN II-III 3/4.All patients have diabetic encephalopathy I-II
Conclusions
1) For patients with DM 2 on IIT among risk factors of symptomatic hypoglycemia we found the AH and DN, for DM 2 on CT – AH, DN, BMI – 36.6 ± 1.4/31.6 ± 1.2 for men and women. 2) For patients with DM2 on ITT and CT among risk factors of symptomatic hypoglycemia we found diabetic encephalopathy I-II.

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EP56

An uncommon case of diabetic mastopathy

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Objective
Diabetic mastopathy (DMP) is an uncommon fibrous disease of the breast, most commonly found in premenopausal women with type 1 diabetes exposed to long-standing insulin therapy. Often mimicking breast cancer clinically and on imaging, this condition poses a diagnostic challenge requiring pathological confirmation.
Case presentation
A 68-year-old woman with type 1 DM and a family history of breast cancer in paternal aunt had an abnormal screening mammogram showing a lobular nodular density in the subareolar region deep to the nipple measuring atleast 2.5 cm in the left breast. Ultra Sound (US) showed a hypoechoic, heterogenous mass 2 cm from the nipple, measuring $41\times13\times46$ mm with relatively circumscribed margins, demonstrating some internal blood flow on Doppler. Lymph nodes were normal. Patient underwent US-guided biopsy. Pathology showed hyalinized stromal fibrosis and chronic mastitis. Within a short period of time, patient presented with a painless palpable area in the right breast. Mammography and US of right breast showed a very dense tissue in the palpable area of concern, corresponding to heterogeneous, slightly hypoechoic mass with relatively circumscribed margins measuring $38\times18\times65$ mm with internal vascularity. It had a very similar appearance to the area that was biopsied on the left breast. Given the bilaterality and history of diabetes, a preliminary diagnosis of bilateral diabetic mastopathy (DMP) was made. A decision was made to follow up annually with regular mammography. Later, patient developed retraction in the skin and nipple areolar complex in both breasts. Mammogram and US of both breasts revealed large densities that were relatively stable, however the skin changes prompted repeat biopsies. Thickened tissue on both breasts was excised and sent for pathology revealing features consistent with DMP.
Discussion
Patients with DMP clinically present with painless, irregular, hard, unilateral or bilateral breast masses. It is rare as it represents 0.6% to 13% of benign lesions observed in woman with type 1 diabetes. The pathogenesis is not fully understood but many theories involving the effects of sustained hyperglycemia and glycosylated end products on the connective tissues of the breast have been proposed. Malignant transformation has not been described.
Conclusion
This case underlines the importance of considering diabetic mastopathy in the differential diagnoses when evaluating breast lesions in women with diabetes. Recognizing the presentation of this rare condition can help avoid unnecessary surgical intervention.

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EP57

Dermatologic manifestations ofdiabetes mellitus-diabetic thick syndrome

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A broad spectrum of cutaneous disorders may be diagnosed in patients with type 1 and type 2 diabetes mellitus. Some of dermatologic lesions may precede any clinical or biochemical evidence for diabetes, while others are considered well known complications of the metabolic disorder. We highlight typical, rare dermatological manifestations of diabetes, excluding infectious, disorders related to complications of diabetes mellitus and skin conditions induced by treatment of diabetes. Cutaneous marker for diabetes are important to be recognized rom early stages, although they are rare or misdiagnosed.
We present case series of diabetic thick syndrome classified as follows:
1) clinical asymptomatic
2) hand skin thickening presenting as
- 'waxy skin'
- finger pebbles
- 'velvety' skin over the small joints of the digits
- knuckle pads

3) scleredema adultorum

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EP58

Influence of vitamin D therapy on albuminuria in patients with type 2 Diabetes mellitus

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Background
Vitamin D deficiency has been shown to be a risk factor related to diabetes mellitus (DM). Some studies suggest an association between diabetic kidney disease (DKD) and vitamin D (VD).
Aim
To evaluate the effect of the vitamin D therapy on albuminuria in type 2 DM patients.
Methods
There was a 4-month study (January – April 2017) of 48 participants on stable antihyperglycemic (metformin and/or sulfonylurea) and antihypertensive treatment (including angiotensin II receptor blocker). Patients were randomized into two groups: 24 patients of the Ist group received 2000 IU/day of cholecalciferol for 16 weeks, the IInd group of 24 patients continued antihyperglycemic and antihypertensive treatment. BMI, glomerular filtration rates (GFR), hemoglobin A1c (HbA1c) were estimated. Inclusion criteria: type2 DM patients with HbA1c $\geq$7%; GFR $>$90 ml/min/1.73 m^2, duration of DM no more than 10 years, controlled arterial hypertension. Exclusion criteria were bone metabolism and liver diseases. Serum 25(OH)vitaminD, low-density lipoprotein cholesterol (LDL-C), HOMA-index, urinary albumin excretion rate (UAER) obtained before and after 4-month period of treatment. Quantitative data are expressed as the mean$\pm$S.D. The Student's *t*-test was used to compare data before and after VD supplementation. The correlation between variables was assessed using the Pearson correlation coefficient. All information was processed with SPSS 21.0.
Results
The mean age of the participants was (54 ± 6.8) years, BMI – (30.9 ± 2.41) kg/m^2, HOMA – (6.3 ± 2.30), HbA1c – (7.8 ± 0.85)%, the baseline UAER – (69.8 ± 37.62) mg/24 h, the mean 25(OH)vitamin D – (28.5 ± 5.80) ng/ml, LDL-C – (3.1 ± 0.74) mmol/l. 25 (OH) vitamin D levels were inversely associated with BMI ($r=-0.4$; $P=0.05$), HOMA ($r=-0.7$; $P=0.005$), UAER ($r=-0.7$; $P=0.005$), LDL-C ($r=-0.4$; $P=0.02$). Compared with the IInd group, vitamin D therapy had no significant effect on HOMA, plasma LDL-C concentration and UAER ($P>0.5$). UAER was reduced but only four patients of 24 had their DKD stage improved.
Conclusion
Strong inverse correlation between 25(OH)vitamin D levels and albuminuria can indicate on benefits of vitamin D supplementation for prevention of DKD in diabetic patients. Although cholecalciferol therapy did not decrease urinary albumin excretion rate and LDL-C concentration significantly in patients with diabetic nephropathy the sample size of our study needs to be enlarged to reinforce data.

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EP59

Gender differences in patients with coronary heart disease and diabetes. A retrospective study

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Introduction
There are known biological differences between men and women in coronary heart disease. It is important to know these differences in order to avoid inequalities in prevention, diagnosis and treatment of this pathology.
Methods
We designed a retrospective, descriptive study in which we included all diabetic patients admitted to the hospital with acute coronary syndrome in 2016. Demographic data and degree of control of risk factors were registered.
Results
We studied 132 patients (60.6% men; mean age 68.7 years), 47.7% had a prior acute coronary event. We observed that our female population was older (72.15 vs 68.08 years, $P<0.05$), had more prevalence of high blood pressure (92.3% vs 72.5%, $P<0.05$) and less smoking habit (44.7% vs 55.3%, $P>0.05$). Degree of control of risk factors was slightly better in men group although we did not observe a significant difference (HbA1c $<$7% in 51.3% of men and 46.2% of women; LDL$<$100 mg/dl in 62.5% of men and 53.8% of women). We found a significant difference in lethality between both groups (15.38% of women vs 1.25% of men, $P<0.05$).

Conclusions
As it is described in literature we observed a later development of coronary heart disease in women of our sample and more lethality. The degree of control in our group was unsatisfactory and it was slightly poorer in women. A greater awareness of the differences in presentation of acute coronary syndrome between men and women, with gender-based interpretation of diagnostic tests, is mandatory for health care professionals to improve therapeutic strategies and outcomes in women.

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EP60

Diabetic foot ulcers (DFU) in eastern India: an observational

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Foot ulceration in diabetes is known to represent a major cause of morbidity and mortality, and carry considerable financial implications for healthcare organisations. Little research has studied the outcomes for patients with foot ulcer in Eastern India. We identified 717 patients aged 18 years and over with Type 2 diabetes mellitus (T2DM) who presented for management of their diabetic foot ulcers from February 2013-February 2016 with mean follow up of 2 years. Methods: Of the 717 patients (574 male (71.4%), mean age 56 (range 49–63) years); 645 (89.9%) healed during follow up. We compared risk factors between healed and non-healed ulcers. All patients received standard of care including off loading where appropriate.
Results
There was no difference in age, gender, duration of diabetes and HbA1c and site or number of ulcers on the feet or amputation between healed and non-healed groups; but patients were heavier in the latter group. There was however increased vascular calcification in the non healed group and also higher Wagner grade but more use of total contact casting (TCC). In a multivariable logistic regression analysis the odds ratios for non-healing were: weight (1.02), duration of ulcer (1.27), higher Wagner classification (1.52), vascular calcification (yes/no) (2.21) and use of TCC (2.24).
Conclusion
Calcification of foot arteries, higher grade ulcers, longer duration of ulcer and patient's weight play a role in non-healing. Having a better understanding about the risk factors involved in the non-healing of DFU and treatment strategies provided will help in reducing the prevalence of foot ulcers. Further studies are required to see if these modifiable risk factors need to be looked at to improve wound healing.

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EP61

What is the knowledge of a population of Tunisian diabetic women on the diabetic foot?

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Introduction
The diabetic foot is a public health problem in Tunisia. The objective of our study is to evaluate the knowledge of diabetic patients on this entity.
Material and method
This is a prospective study involving 60 diabetic patients hospitalized at C service of diabetology and nutritional diseases at the National Institute of Nutrition of Tunis. The knowledge of these diabetics was assessed using a pre-established questionnaire.
Results
The mean age was 57.35 years $\pm$ 11.22. The average BMI was 29.45 kg/m^2 $\pm$ 4.55. Diabetes was type 2 in most cases, poorly balanced in all patients with an average HbA1C of 10.23% $\pm$ 1.55. The cardiovascular risk factors associated with diabetes in our patients were: sedentary lifestyle (90%), obesity (76.6%), menopause (61.6%), hypertension (46.6%), dyslipidemia (41%), 6%) and smoking (15%). Only 26.6% of patients received a prior education in foot hygiene. 58.3% associate this foot injury with arterial disease (43.3%) and neuropathy (15%). All patients report foot infection as a triggering factor. The clinical signs according to our patients are: mycotic infections, trolling bacterial infections, amputations, gangrenes and plantar perforators. The mistakes made by our patients were: the lack of daily inspection of the feet (100%),
Conclusion
Regular diabetic foot education sessions are extremely important in teaching patients simple and practical actions that limit potentially serious complications.

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EP62

Predictive factors of hyperuricemia in diabetics Type 2: About 168 cases

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Introduction
Hyperuricemia is common in type 2 diabetics particularly in patients with very high cardiovascular risk.
Objective
To evaluate the relationship between hyperuricemia and type 2 diabetes, and to determine its predictive factors in this population.
Patients and methods
A retrospective cross-sectional study including168 patients with type 2 diabetes who were hospitalized in the endocrinology department of Ibn Rochd University Hospital, Casablanca from January 2015 to January 2017. Hyperuricemia was defined by a serum uric acid concentration $>$70 mg/l (men) and $>$60 mg/l (women). Variables studied were anthropometric measurements), cardiovascular factors (tabagism, hypertension, dyslipidemia) and degenerative complications (retinopathy, neuropathy, renal insufficiency, ischemic heart disease). Analyziswas performed by the SPSS software.
Results
Average age of our patients was 53.8 years (27–81).Hyperuricemia was found in 28% of patients with a clear predominance of women (78.9%, $P<0.30$), an average age of 56.5 years, and a mean diabetes duration of 12.3 years. Glycemic imbalance was found in 84.6% of the cases with a glycated hemoglobin average of 8.4% ($P<0.30$). Predictive factors prevalence for hyperuricemia were smoking objectified in 7.6% of patients ($P<0.90$), obesity in 62.1% ($P<0.10$), which was moderate in 22.5% ($P<0.20$) and morbid in 20.3% (p <0.30). 85% of patients were hypertensive ($P<0.05$), 80.3% were dyslipidemic ($P<0.001$) with hypertriglyceridemia in 58.3% of cases ($P<0.02$), and hypoHDLemia in 38% ($P<0.001$). The search for degenerative complications related to hyperuricemia showed retinopathy in 52.8% of patients ($P<0.10$), neuropathy in 28.6% ($P<0.9$), renal failure (GFR between 15 and 60 ml/min) in 53% ($P<0.001$), which was moderate in 42.8% ($P<0.01$) and severe in 11.1% ($P<0.02$). Ischemic heart disease was found in 45.8% of cases ($P<0.01$).
Discussion
In our study, hyperuricemia in type 2 diabetic patients is common in female patients, particularly with hypertension, dyslipidemia and renal failure. Other factors such as age, obesity, smoking are not related to hyperuricemia in type 2 diabetics.

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EP63

Sympathetic hyperactivity and sleep disorders: is Type 2 diabetes the link between these two situations?

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Results
Main clinical, analytical and polygraphic data: 58.1 $\pm$ 6.4 years, body mass index 32.4 $\pm$ 5.4 kg/m^2, 70.4% female, HbA1c 8.0 $\pm$ 1.9%, AIH 27.4 events/hour (in the range of severe sleep apnea and hypoapnea index), and CT90% 32.9%. Nocturnal concentration of urine total metanephrines were higher than diurnal levels (226 $\pm$ 12 vs 98 $\pm$ 13 µg/l; $P=0.085$). In addition, its nocturnal concentration was significantly associated, in a positive way, with both the AIH and the CT90;

however, this association disappeared when the diurnal concentration was evaluated. Furthermore, nocturnal concentration was also associated with a decrease in resting parasympathetic tone. In the multivariate analysis, the concentration of urine metanephrines at night independently predicted CT90 ($P=0.016$).

Conclusion

We suggest that the increased sympathetic activity previously described in patients with T2D is mediated through the deleterious effect of diabetes in nocturnal breathing. In addition, sympathetic activity is associated with disorders of autonomic tone at resting, suggesting a new pathological pathway between T2D and cardiovascular risk.

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EP64

Awareness of gestational diabetes, its risk factors and its consequences among tunisian pregnant women

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Introduction

The prevalence of Gestational diabetes mellitus (GDM) has been increasing recently. Educating women of childbearing age about GDM, its risk factors and complications may help its prevention and improve its outcomes. Hence, the aim of this study was to assess the level of knowledge of Tunisian pregnant women about gestational diabetes, its risk factors and its consequences.

Methods

We conducted a cross-sectional study among pregnant women who were referred to the National Institute of Nutrition for management of GDM. Women without prior diabetes mellitus were included. Qualitative semi-structured interviews were conducted to collect their socio-demographic characteristics and to assess their knowledge about gestational diabetes, its risk factors and its consequences. Data of biological examinations were collected from medical files of patients.

Results

The study included 30 pregnant women of average age 33.6 ± 5.3 years. Approximately 37% of women were primiparous. Overweight (body mass index ≥ 25 kg/m^2), diabetes mellitus in first-degree family members and advanced age (≥ 35 years) were prevalent risk factors in our population (73%, 60% and 57% respectively). Quarter of women had a past medical history of GDM and only 3% reported a previous history of macrosomia. More than 75% had completed at least secondary school education. Less than half of women (47%) didn't have an idea about GDM. However, 43% of the population knew that GDM is a transitory hyperglycemia which occurs in pregnancy. Other definitions as transitory pancreatic dysfunction or as feeling of hungry or as asthenia were reported. The most commonly reported risk factors of GDM were high carbohydrate intake (80%) and psychological stress (40%). Only 6% of women knew that overweight and family history of diabetes can be predictive factors of GDM. Consequences of GDM weren't well known for the majority of our patients. Macrosomia and malformations were identified as GDM consequences by 33% and 27% respectively. Sixty percent were worried about causing diabetes to the fetus. Also, many women (43%) didn't know the increased risk for development of Type2 diabetes in future.

Conclusion

In this study, the majority of women had limited knowledge of gestational diabetes, its risk factors and its consequences. Furthermore, it was interesting to report that Tunisian pregnant women thought that stress increased the risk of developing gestational diabetes. The improvement of awareness of GDM since the preconception period can be useful to reduce the prevalence of this type of diabetes and to incite pregnant women to better take care during all their pregnancy.

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EP65

Characteristics of insulin-requiring diabetes among elderly patients in hospitals

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Introduction

Diabetes in the elderly is a major public health problem in Tunisia. Its prevalence increases with aging population. The aim of this study was to determine the particularities of insulin-requiring diabetes in elderly patients in hospitals.

Methods

This was a retrospective cross study about insulin-treated diabetics admitted in our institute between August and October 2016 for uncontrolled diabetes. Was considered as elderly diabetic any patient of 60 years and older. Data about medical history, comorbidities and clinical examination were collected from medical file of patients.

Results

This study included 132 patients with insulin-requiring diabetes. Patients aged 60 and older accounted for 37.8% of cases ($n=50$). The mean age was 69 years (raging 60–84 years). Sex ratio(F/H) was 0.56. The mean number of years since diagnosis of diabetes was 17.6 years with extremes ranging from 3 months to 42 years. Insulin therapy was initiated for an average of 8 years. The incomplete basal bolus regimen was the most prescribed (40%). Only 16% of patients were on insulin analogues and half of them were over 75 years old. One third of the patients reported hypoglycaemia. None of them were under analogues. The significantly more frequent complications in elderly patients than in younger ones were: retinopathy (69% vs 45%, $P=0.01$), neuropathy (62% vs 44%, $P=0.005$) and nephropathy (58% vs 28%, $P=0.01$). One third of patients was treated for a coronary artery disease and 10% had cataracts. Dyslipidemia, arterial hypertension and obesity were observed in 80, 68 and 50% of elderly diabetics, respectively.

Conclusion

The typical profile of our elderly population was that an obese type 2 diabetic woman at high cardiovascular risk. The frequency of hypoglycaemia and the high prevalence of degenerative complications in our diabetic elderly population can lead to a loss of autonomy.

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EP66

Alterations in intestinal microbiota and arginase activity in leukocytes of type 1 diabetes patients

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Type 1 diabetes mellitus (T1DM) is one of the most frequent autoimmune disorders in childhood, adolescence and youth, developing due to autoimmune destruction of pancreatic β-cells, which leads to an absolute insulin deficiency. Gut microbiota (GM) is associated with the functions of the body's immune system, and immune-mediated diseases, including T1DM. However, the exact mechanisms by which GM is involved in the T1DM are still unknown. Accumulating data suggest that GM may contribute to the pathogenesis of diabetes influencing the immune response, in which arginine-metabolizing enzymes are involved, particularly arginase. Here, we examined the connection between gut microbiota and cytoplasmic and mitochondrial arginase isoforms (AI and AII respectively) in the leukocytes of patients with T1DM. The A1 activity is necessary to protect M2 macrophages from inflammation, it is constitutively expressed in human neutrophils and exhibits fungicidal activity, whereas A2 is involved in the production of reactive oxygen species implicating in the oxidative stress and inflammatory processes involved in the T1DM pathophysiology. This offers that arginases can be therapeutic targets in T1DM, and this issue is studied in the presented work. Arginase assay was based on the accumulation of L-ornithine produced by arginase in the reaction mixture during 1-hour incubation and determined by means ninhydrin. Measurement of the nitric oxide stable metabolites in protein-free samples was performed using Griess-Ilosvay reagent. Number of *E. coli* and Clostridium spp were drastically decreased with a concomitant increase in that of *Candida albicans*, and a manifestation of *Staphilococcus aureus* was also observed in T1DM, which may compete with the gut beneficial bacteria. Of note, *E. coli* and Clostridium *spp* play a protector role for GM, whereas clinical cultures of *C. albicans* has detrimental effects causing desquamation of small fragments peptidoglycan layers of cell wall and total destruction of the cytoplasm in lactobacilli. The arginase activity was increased by 2 and 1.6 times in the cytoplasm and mitochondria of leukocytes from T1DM patients as compared respectively to control. Arginase is known contribute to decreased availability of L-Arginine in the organism, and particularly to nitric oxide synthase that may cause a subsequent reduction of NOS/NO production attributed to the pathological processes associated with diabetes. Based on this, the nitrite levels in the leukocyte cytoplasm, mitochondria and blood plasma were examined and in line with other findings it was dropped by 1.9, 2.3 and 1.6 times respectively.

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EP67

Reduction of glycemic variability in a patient with type 1 diabetes with hipoglycemia

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The routine approach to evaluating the effectiveness of diabetes treatment based on the level of glycated hemoglobin (HbA1c) accounts for the average glucose level but does not consider its fluctuations. However, recent data indicate that the development of late complications of diabetes is associated with the degree of variability in glycemia. (GV).

Clinical case

Patient F. is 54-year-old woman with a 33-year history of type 1 diabetes with multiple chronic complications: Diabetic autonomic neuropathy (unrecognized hypoglycemia). Diabetic sensorimotor polyneuropathy. Non-proliferative diabetic retinopathy. Diabetic nephropathy, CKD C2A1. There were frequent hypoglycemic episodes in the night and morning hours, including two unrecognized episodes requiring hospitalization. She tests her glycemia rarely, according to glucose meter from 1.7 to 14.0 mmol/l. But, the level of HbA1c from December 2017 is 7.3%. She received insulin therapy: insulin lispro 12 IU at 0800 h, 8 IU at 1800 h, insulin glargine 10 IU at 1000 h, 12 IU at 2200 h. Continuous glucose monitoring with the iPro-2 Medtronik (USA) system was carried out for a detailed study of glucose curves for 6 days. The increase in glycemia in the morning was recorded more than 22.2 mmol/l. Also episodes of lowering to 4.5–3.2 mmol/l, both clinically recognized and not recognized. Data analysis was carried out using the Easy GV calculator (v.9.0), proposed by N.Hill et al. We found a deviation in the parameters of GV: standard deviation SD 4.25 mmol/l (3,0), mean amplitude of glycemic excursions MAGE up to 5 mmol/l (2.8), lability index LI 5.85 $(mmol/l)^2/h$ (4.7), the continuous overlapping net glycemic action CONGA 11.39 mmol/l (5.5), the M-value index 31.21, which characterizes the "quality" of glycemic control. Therapy with long-acting insulin was started – glargin-300. The drug is chosen taking into account its longer period of action, gradual release from the subcutaneous fat, less variability of the action. The total dose of glargin-300 was 14 units (decreased by 8 units), GV during the day – from 6.5 to 13.0 mmol/l. Hypoglycemic episodes were not observed.

Conclusion

The choice of therapy taking into account the characteristics of GV allowed to achieve a decrease in the amplitude of fluctuation in glycemia, thus improving the long-term prognosis. Insulin glargin-300 may be the preferred drug in patients with type 1 diabetes and high GV, regardless of the level of HbA1c.

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EP68

Diabetic ketoacidosis and dapagliflozin: a case report

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Introduction

Dapagliflozin is an oral antidiabetic drug, recently approved for type 2 diabetes and is a sodium-glucose cotransporter type 2 inhibitor (iSGLT2). Its mechanism of action is glycosuria induction, associated with lowering glycemia. The effects of SGLT2 inhibition are insulin-independent, and efficacy is not affected by declining β-cell function or insulin resistance. Additional benefits: weight loss, reduction in blood pressure, lower incidence of hypoglycaemias. Secondary effects: diabetic ketoacidosis risk (in some cases, euglycemic ketosis), in type 2 diabetes and type 1 diabetes (in the last case, when used off-label).

Objective

To show the risk of diabetic ketoacidosis in patients treated with iSGLT2, particularly in type 1 diabetes.

Case report

A 82 years-old woman**,** with more than 50 years diabetes diagnosis, associated with microvascular and macrovascular complications (coronary disease, diabetic neuropathy and retinopathy); treated with insulin at the diagnosis. Classified always on type 2 diabetes. She presented at the emergency service with two days of headache, anorexia, nausea, abdominal pain. Previously, the patient had been evaluated and treated with analgesia and proton pump inhibitor. Physical examination at the emergency service: dehydration, tachycardia and abdominal pain. Laboratory findings: hyperglycaemia (556 mg/dl), acidosis (pH – 7.21, HCO3 – 9.8 mEq/l), positive ketone test (5.7 mmol/l), acute renal failure (creatinine: 1.86 mg/dl, basal creatinine 0.5 mg/dl), leucocytosis (19.3 G/L) and negative C-reactive protein. It was diagnosed a diabetic ketoacidosis and the patient was hospitalized with continuous insulin infusion and fluids. Further investigation showed recent onset of dapagliflozin (10 mg/day). Other medication: Abasaglar ® id, metformin (1000 mg 3id) and sitagliptin (50 mg 2id). Laboratory findings: haemoglobin A1c – 11.1%, c-peptide 0.2 ng/ml (1.0–7.6 ng/ml), ICA – positive, GADA – 79.81 U/ml (<1.0) and IA-2 – 0.16 U/ml (<1.0). After clinical stabilization, the patient was discharge with insulin (NovoMix 30®, 3id). Dapagliflozin and others oral antidiabetic drugs were stopped.

Discussion and conclusion

The present case pretends to show the risk of diabetic ketoacidosis in both type 1 and type 2 diabetes, particularly in type 1 diabetes. So, when hyperglycaemia and/or ketosis symptoms are present, it is essential to perform ketone test and gasometry. It is important to know that patients treated with iSGLT2, may have mild hyperglycaemia, even in diabetic ketoacidosis. This case is also intended to show that a considerable rate of patients, classified with type 2 diabetes, have effectively an autoimmune diabetes.

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EP69

When is it possible to withdraw insulin in patients with type 2 diabetes and multiple cardiovascular risk factors? Can the new drugs be of help?

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Introduction

Insulin is not an optimal treatment in obese type 2 diabetic patients with insulin resistance. We often introduce it as a last resort hoping to improve the metabolic control of our patients. However it is not always effective, and tends to increase body weight, worsen the global cardiovascular risk and cause hypoglycemias. New drugs such as the GLP-1 agonist receptors can be a better alternative and sometimes allow withdrawal of insulin.

Clinical case

A 59 year old female patient had morbid obesity (BMI 41 kg/m^2) and type 2 diabetes mellitus diagnosed 17 years ago, chronically poorly controlled (HbA_{1C} > 8% in the last 10 years) with metformin 850 mg TID and insulin in escalating doses up to 36 units of 75NPH/25R premix TID. She also had hypertension, chronic coronariopathy with anterior AMI diagnosed five years ago and successive heart failure with preserved ejection fraction and paroxystic atrial fibrillation. Her treatment included Atenolol 50 mg BID, Olmesartan 40 mg, Amlodipine 10 mg, Hydrochlorothiazide 25 mg, Doxazosine 4 mg and acenocumarol. She was admitted in Internal Medicine because of decompensated heart failure in the context of a respiratory infection. Her HbA1c was 8.6% and eGFr CKD-EPI 82.2 ml/min, with LDL-cholesterol 72 mg/dl. On discharge she was offered treatment with Liraglutide but chose Dulaglutide 1.5 mg/week. Metformin was maintained and the insulin dose was reduced to 20-20-14 units. Four months later she had reduced the dose to 19-19-13 because of mild hypoglycemias and her HbA1c was 6.1%. She had lost 9 kg of body weight. After three months her dose was 12-12-6 with HbA_{1C} 5.8% and LDL-cholesterol 56 mg/dl. Sixteen months after discharge she maintains a body weight loss of 10 kg, insulin was withdrawn while maintaining adequate glycemic control, her HbA_{1C} was 6.8%, and her antihypertensive treatment was reduced (Olmesartan 20 mg, Bisoprolol 2.5 mg substituted for Atenolol 50 bid, and Hydrochlorothiazide withdrawn). Moreover, the patient was quite satisfied with her evolution.

Conclusions

The new therapeutic arsenal for type 2 diabetes mellitus, particularly the SGLT2 inhibitors and the GLP-1 receptor agonists, have improved our ability to achieve

metabolic control in obese patients with marked insulin resistance, and in many cases may avoid the introduction of insulin and even allow its withdrawal in patients such as ours. We must also consider the positive results of trials like EMPA-REG OUTCOME, CANVAS and LEADER in secondary cardiovascular prevention.

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EP70

Controversies of endocrine treatment in Prader-Willi syndrome: a case report of two monozygotic twins

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Introduction
Prader-Willi syndrome (PWS) is a neurobehavioral imprinting disorder, which arises due to an absence of paternally expressed genes within the 15q11.2-q13 region. It is the most common syndromic form of obesity, with an estimated prevalence of about 1 in 25,000 individuals.
Case report
we report the case of two monozygotic twins, 20-year-old, naturally conceived, both affected by PWS. They were born by eutocic delivery at 34 weeks of gestation and somatometry was appropriate for gestational age. Both presented neonatal hypotony, feeding difficulties, psychomotor delay, characteristic facies and cryptorchidism. Genetic test confirmed maternal uniparental disomy of chromosome 15. From 4 years of age they presented progressive increasing weight (percentile > 95) associated with binge-eating but delayed height growth (percentile 10-25). Orchidopexy was performed at 5 years of age. Puberty started at 12 years but did not progress. At 16-year-old, treatment with testosterone enanthate monthly injections and recombinant human growth hormone (rhGH) was started. Despite dietetic measures, both twins developed insulin resistance and morbid obesity (body mass index: 49.8 and 44 kg/m^2) due to marked hyperphagia. Furthermore, they had obstructive sleep apnea, cognitive delay and behavioral problems (temper tantrums, stubbornness, impulsivity, aggressiveness), which ultimately led to the cessation of treatment with testosterone. Worsening of obesity and sleep apnea at the age of 19 dictated the stop of rhGH.
Conclusion
To our knowledge, very few cases of naturally conceived twins affected with PWS were reported. Endocrine treatments can be controversial in these patients, because of a possible exacerbation of behavioral problems and other comorbid conditions.

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EP71

Evaluation of diabetes and cardiovascular risk factors in a population of diabetic patients in a rural area

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Introduction
Diabetes is a real problem of public health. One of the main preoccupations that arises from it are the cardiovascular complications that are associated to it. In our context, the socioeconomic conditions and the isolation of certain regions constitute a brake that cannot be neglected in the diagnosis, the observance of the treatments and the regular supervision. The aim of this study is to raise the particularities related to the cardiovascular risk factors in the population of a rural region.
Patients and method
Transversal descriptive study, realized on a health campaign day in the rural region of Imessouane (82km far from Agadir) and concerning diabetic patients of the region. The anthropometric parameters, the glycemic balance and the cardiovascular risk, using the NHAES score, have been evaluated.
Results
The average age was 52.2 years with a feminine predominance. Type 2 diabetes has been found in 98.4% of the cases, the average duration of the diabetes was 5.1 years. Also, 72.9% of the diabetic patients were under oral treatment and 72.9% consulted a doctor regularly for their diabetes. The average glycated hemoglobin was 7.9%. The hypertension and the dyslipidemia were found in 29% of the cases. The patients had a regular physical activity in 68% of the cases. The cardiovascular risk was above 30% in 31.4%.
Discussion
The access to healthcare keeps being a real problem, especially in the remote areas. The progress of this day enabled as well to evaluate the epidemiological and clinical characteristics of these patients, having access to unique socio-demographic and epidemiologic data as there are almost no studies done in remote areas. The glycemic balance stays precarious as the follow-ups are non-sufficient. In our rural population, very active by their agricultural activities, the cardiovascular risk is lower than some similar studies done in the same conditions but to a more sedentary population.

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EP72

Type 2 diabetes: an unexpected journey

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We report a case of a well 40 year old gentleman who self-referred for confirmation of diagnosis of diabetes. On further history he had been informed by other healthcare professionals the possibility of diabetes based on his elevated fasting serum glucose of 13.8 mmol/L and HbA1c of 81mmol/mol with no osmotic symptoms. His triglyceride was also elevated at 12.26 with rather variable compliance to statin. Examination of all systems were unremarkable, however on neck examination both thyroid lobes were palpable. Right lobe felt irregular and nodular, and left lobe smooth. It was rather difficult to palpate the lower pole of the thyroid lobes. No thyroid or carotid bruits audible; no lymphadenopathy felt. The patient was clinically euthyroid. Ultrasound of neck and thyroid was arranged and showed pathological level III lymph nodes and an indeterminate hypoechoic left thyroid nodule with possible areas of micro-calcification; U3 thyroid nodule. Subsequently, an MRI of the neck confirmed a single morphologically abnormal lymph node at level IV on the right. FNA of the left thyroid nodule was suspicious of papillary neoplasia and FNA of the right cervical node was suggestive of metastatic carcinoma. The patient underwent a total thyroidectomy with an uneventful recovery. He was commenced on thyroxine and calcichew D3. He is awaiting I131 therapy. This case emphasises thorough history and examination is crucial for patients wellbeing which may well improve comorbidities and prolong one's life.

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EP73

Clinical case of late diagnosed diabetes in ketoacidotic coma III in teenager: lessons to be learned

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Patient Z., 13 years old, transferres to the ICU with diagnosis: Diabetes mellitus newly diagnosed. Diabetic ketoacidotic coma II. Concomitant: Left-sided pneumonia.
Objective
Cussmaul's breath, 36/minute. Pulse 128/min. BP 100/60 mm Hg. Glycemia 30.4 mmol/l, ketones in urine: $++++$. CBC, urine, biochemical analysis of blood had not any special features. In the dynamics of the phenomenon of increasing respiratory failure and falling hemodynamics, the patient was intubated, pulmonary ventilation was started in the SIMV mode, inotropic support started. Lungs: left-sided upper-lobe large-focal pneumonia, Pseudomonas Aeruginosae was found in the sputum. The patient was admitted with extremely severe dehydration, disturbed microcirculation, including violation of renal blood flow, which was reflected in diuresis inadequate to glycemia. Infusion therapy was carried out under strict control of CVP and diuresis, however, CVP was negative during the first two days. The speed of infusion therapy was 15 ml/kg/h for the first 24 h, 11.4 ml/kg/h during the following 24 h, followed by a decrease to 7–8 ml/kg/h at the 3rd and 4th days, 6 ml/kg/h at the day 5. On the fourth day the introduction of fluids through the nasogastric tube, and on the 5th day feeding was started. The decrease in glycemia during the first day was down to 13 mmol/l, on day 2 - to 7.8 mmol/l. Ketonuria was eliminated by the 2nd day.

Insulin infusion rate during the first day was 0.2 units/kg/h during the first 6 h, but as this dose was insufficient, it has been raised to 0.38 U/kg/hr during the 2nd day, 0.1 unit/kg/h for the first 12 h of the 3rd day, with gradual decrease during the next day to 0.07–0.06–0.04 units/kg/h. Long acting insulin was added on the 6th day of treatment. At the time of discharge, the daily dose of insulin was 13 units. Potassium solutions were administered according to international recommendations. The reasons for the development of a critical life-threatening condition in this patient are: late admission; late diagnostics; the presence of severe competing diseases - left-sided large-focal pneumonia, bilateral acute purulent otitis media; excessively high insulin requirements associated with puberty. Patient was checked out in 1 month for reabilitation and diabetes education.

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EP74

Role of the dentist in managing obese patients and patients with diabetes mellitus – why oral health matters?

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Physicians and dentists have long known that the health of an individual's mouth can have significant effects on the health of the rest of the body. Researchers are finding more medical reasons to maintain good oral hygiene. Numerous recent scientific studies indicate association between oral health and a variety of general health conditions including diabetes and obesity. Studies have suggested a bidirectional relationship between periodontitis and diabetes and periodontitis and obesity. Diabetes and obesity promote the occurence, the progression and the severity of periodontitis. Conversely, periodontitis was shown to be a risk factors for poor glycemic control in patients with diabetes due to bacteria and their byproducts in the inflammed periodontal tissue constituting a chronic source of systemic chalenge to the host, increases the risk of diabetes-associated complications and possibly even of ist onset. Some studies suggest mechanisms by which oral bacteria may contibute to development of obesity by increasing apetite and changing of diet habits and redirecting energy metabolism by facilitating insulin resistance through increasing levels of TNF-α or reducing levels of adiponectin. Tooth loss due to periodontitis seriously decreases chewing abillity which is related to quality of life and general health, possibly reflecting the impact on chewing food choice and enjoyment of meals and diet and also indicated the importance of oral health to general well-beeing. It is still not sufficienty communicated within the medical community, because the periodontal disease is stil considered as the concern of only dentists. Physicians and dentists need to be aware of the relationship between periodontitis and diabetes and take adaquate steps to minimaze negative outcomes in patient with diabetes mellitus or obese patients.Periodontal therapy which decreases the intraoral bacterial bioburden and reduces periodontal inflammation can have a significant impact on systemic inflammatory status and improves glycemic control in many patients with diabetes and periodontitis. Recognition of the bilateral relationship between oral and systemic helath will chalenge physicians and dentists to work together closely in the future when managing patients with diabetes and periodontal disease. The entire dental team, working together with medical colleagues, must become increasingly involved in the management of patients with diabetes and perform periodontal screening as a matter of routine of all patients diagnosed with diabetes mellitus and periodontitis.

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EP75

Mucormycosis in a patient with diabetes and orbital trauma

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Introduction
Mucormycosis is a serious fungal infection, It is frequently observed in immunocompromised patients such as diabetes mellitus. The most common clinical presentation of mucormycosis is rhino-orbita- cerebral infection.

Case presentation
A seventy three-years- old man with diabetes mellitus who was operated due to orbital trauma a mounth ago. Periorbital cellulitis and diabetic ketosis developed during post-operative period and the patient was transferred to the endocrine clinic. Orbital and paranasal computed tomography were performed, and then necrosis areas were observed in the nasal cavity, middle and lower concha. Mucormycosis was considered with present findings. Surgical debridement and AmphotericinB treatment were started. Pathologic examination confirmed mucormycosis. Despite surgical debridement and amphotericin B treatment infection could not be controlled and he was referred to the upper center for hyperbaric oxygen therapy.
Conclusion
The evaluation in terms of mucormycosis may be important in a patient with diabetes mellitus and orbital trauma for early treatment approaches. However, treatment response may not always be good despite early diagnosis.

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EP76

From severe metformin-associated lactic acidosis to colorectal cancer diagnosis, case-report

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Introduction
Metformin is recommended as the first-line pharmacological agent for patients with diabetes mellitus type 2. Its most feared adverse effect is the metformin-associated lactic acidosis (MALA), which appears rarely, but the mortality risk reaches almost 50 percent. This case report describes a story of a severely metformin intoxicated patient with several rare complications and uneven outcome.
Case-report
A 74-year-old man was found at home, unconscious, spontaneously breathing, hypotensive and hypoglycemic. He was admitted to ICU on vasopressor treatment. Major laboratory findings were severe metabolic acidosis including severe hyperkalemia, hyperlactatemia (maximal level of 12 mmol/l), severe renal impairment (eGFR 5 ml/min/1.73m^2), troponin T (84 ng/l), CRP (31 mg/l), leukocytosis (22×10^9), anemia (80g/l), metformin level (34.2 ug/ml). Initially acute coronary syndrome, pulmonary embolism, acute sonographic pathology of the urological tract were excluded and renal replacement therapy (RRT) was necessary for suspect metformin intoxication. After stabilization, he was transferred to a standard internal ward. According to prior patients history, his regular medication was metformin 2 g/day and glimepiride 4mg/day. His last documented laboratory results were normal renal functions, normal blood count one year ago. After 14 days on RRT was the patient still anuric, so the postrenal obstruction was suspected. Ultrasound-guided percutaneous bilateral nephrostomies were inserted with a prompt effect and restoration of diuresis and reparation of renal functions. An X-ray pyelouretrography showed bilateral ureteral obstruction without concrement involvement. An abdominal contrast CT scan revealed a tumor suspect formation in colon ascendens. Via colonoscopy, a diagnosis of colorectal cancer was established and it explained the initial anemia, despite its laboratory findings typical for anemia of chronic diseases. A rare complication appeared, a late onset of heparin-induced thrombocytopenia (HIT), 16th day after initiation of heparin administration, for which the patient had to be anticoagulated with therapeutic doses of Fondaparinux for a HIT-associated deep vein thrombosis of the left leg and mild pulmonary subsegmental embolism. Even though there was no suspect liver metastasis on the CT scan, during the surgery a peritoneal carcinosis was found and so palliative ileotransversoanastomosis was done, concomitant oncological treatment was not planned. A bilateral postrenal extraluminal obstruction due to disseminated colorectal carcinoma was settled.
Conclusion
A case of quickly silently growing colorectal cancer of colon ascendens was described, which in one year resulted in bilateral postrenal obstruction, which led to chronic metformin overdose and sudden severe lactic acidosis.

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EP77

Diabetic ketoacidosis and myocardial 'pseudoinfarction'

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A 68-year-old lady was admitted with constipation, epigastric pain, vomiting, occasional coffee ground emesis and melena. She had no chest pain, osmotic symptoms or weight changes. Past medical history was significant for peptic ulcer disease and she was not taking any medications apart from over the counter cod liver oil. She did not have diabetes or cardiovascular risk factors. Her sister had type 1 diabetes. Examination was remarkable for dehydration, mild tachycardia and melena on rectal examination. Blood tests including haemoglobin, clotting, renal function, electrolytes were normal. Glucose was 37 mmol/l, ketones were 4.3 mmol/l and there was mild acidosis. She was treated with intravenous fluids, intravenous insulin, proton pump inhibitors and anti-emetics. Electrocardiogram (ECG) showed deep T wave inversions in infero-lateral leads. Cardiac enzymes repeated many times were normal, chest X-ray was normal and echocardiogram revealed normal left ventricular function. ECG changes resolved in 24 h. She was diagnosed to have diabetes with high glycated haemoglobin, negative diabetes auto-antibodies and raised C-peptide level, and was commenced on subcutaneous insulin and metformin. Oesophago-gastro-doudenoscopy suggested mild gastritis. ECG changes in diabetic ketoacidosis (DKA) usually signify cardiac ischaemia or electrolyte abnormalities. Abnormal ECG in absence of the above causes in patients with DKA is reported in literature and has been termed as 'pseudoinfarction'. The ECG changes may include ST-segment elevation or depression, T-wave changes and can be non-specific. It is postulated that the acidosis causes change in myocyte cell membrane permeability leading to electrolyte shifts across the membrane with resultant abnormalities in electrocardiogram. The abnormalities tend to resolve with the resolution of acidosis. All patients with DKA and chest pain or ECG changes should have standard assessment with cardiac biomarkers, electrocardiographic monitoring, if appropriate, echocardiogram and coronary angiogram. Cardiology consult should be obtained in suspicious cases but clinicians should be mindful that ECG abnormalities in DKA are not always sinister.

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EP78

Childhood granuloma annulareas first sign of diabetes mellitus: case series

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Ganuloma annulare (GA) is a self-limited inflammatory dermatosis, clinically characterized by the presence of papules arranged in annular or circinate pattern, mostly on the extremities. GA has rarely been reported in childhood, although is a not a rare condition seen in adulthood. Aetiology and pathogenesis of GA are still unknown, although variable associations have been reported, during last decades, with diabetes mellitus, thyroid disorders, HIV infection, malignancies, tuberculosis, Epstein Barr and hepatitis C virus infection or drug administration. Controversial statistically correlation between GA and diabetes mellitus has been published in the literature. We present cases of GA diagnosed in children (based on clinical and histological features) with diabetes mellitus at the moment of diagnosis or diagnosed later and similar cases in children without diabetes mellitus. GA was in a few children a "cutaneous marker" for a newly detected diabetes mellitus. GA patients should be assessed for diabetes mellitus even in children. More studies and reports are needed for establishing the real link between GA and diabetes mellitus.

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EP79

Parapharyngeal abscesses of dental origin in diabetics

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Introduction
Parapharyngeal abscesses develop at the pharyngeal lateral wall. It is a rare infectious complication. The starting point is most often a pharyngeal infection that extends through the fibers of the upper constrictor muscles of the pharynx. The dental origin is more rare. It raises the problem of therapeutic management. The aim of this presentation was to detail the clinical diagnostic aspects of parapharyngeal abscesses in diabetics and to detail the therapeutic modalities.
Methods
We report a series of 10 patients treated in our ENT department over a period of 8 years (from 2009 to 2017).
Results
They are 8 men and 2 women, aged from 23 to 65 years old. One patient was diabetic type 1 and the other was type 2 insulin-requiring in 5 cases. The reason for consultation was painful dysphagia associated with limitation of mouth opening. Outpatient treatment with antibiotics and anti-inflammatories was given in 3 cases. The examination noted in all cases a trismus, a bad dental state and a parapharyngeal bulge. In the CT scan, parapharyngeal abscesses of varying size and extent were present. The puncture returned serosities and the bacteriological examination was negative in 2 cases. The etiological investigation had concluded to a dental origin. The treatment was medical (intravenous antibiotic therapy, optimal equilibration of diabetes), surgical (flattening of abscess by the oropharyngeal route in all cases) and treatment of the causal tooth.
Conclusion
The treatment of parapharyngeal suppurations is medico-surgical and necessarily involves the treatment of the infectious center in question. Untreated, they provide serious complications including vascular thromboses and extensive cellulite that can be life-threatening.

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EP80

Mental health and diabetes – are we doing enough for our patients?

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Background
Managing mental health patients with Diabetes Mellitus can be challenging. Patients with mental health problems are poorly compliant with both antipsychotic and diabetes treatment. Literature has suggested that some psychiatric illnesses can be independent risk factors for diabetes. Furthermore, diabetic patients have a higher incidence of psychiatric disorders. There is a causal relationship between newer antipsychotic medications and metabolic abnormalities.
Cases from two hospitals
1. 72 year old lady was admitted after being found on the floor in the psychiatric unit. On admission, her glucose was 56 mmol/l with ketonuria. She was treated as Diabetic Keto-Acidosis (DKA). She was on olanzapine.
2. 43 yearold lady was admitted with glucose of 38 mmol/L. Her HbA1C was 160 mmol/mol. She was treated as hyperosmolar hyperglycaemic state (HHS). She was on amisulpride.
3. 38 year old lady admitted with increased confusion, her glucose was 76mmol/L. Complicated by an acute kidney injury, sepsis and acidosis; she was treated as DKA. She was on olanzapine
4. 36 year old lady was admitted after general decline in health. She had a glucose of 73.3 mmol/L and was acidotic. She was treated as DKA. She was on olanzpine and amisulpiride.

Discussion
Olanzapine, clozapine and amisulpride are known as novel antipsychotics. The British National Formulary states diabetes and hyperglycaemia are side effects of antipsychotics. Olanzapine and clozapine have the highest propensity to induce hyperglycaemia. The time taken for clinical manifestations of hyperglycaemia varies from days to years. Poor compliance leads to recurrent hospital admission especially in patients with both conditions. The recent introduction of Abbot's Freestyle Libre has transformed glucose monitoring. Its simplicity may play a vital role in patients with psychiatric disorders. The use of insulin pumps in patients with mental health remains debatable.
Conclusion
- Patients on antipsychotics should be monitored for hyperglycaemia.
- We recommend if one is commencing an antipsychotic in a patient then the assessment for diabetes should take place at initiation, at 3–4 months and annually.
- Physicians must be made aware of the growing association between atypical antipsychotics, diabetes and hyperglycaemic crises.
- Managing diabetes in patients with psychiatric disorders requires an integrated multidisciplinary approach involving both primary and secondary care teams.

- We suggest that clinicians encourage the use of technology such as flash glucose monitoring together with support from family or carers to improve compliance and diabetes care in this special group of patients.

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EP81

Calculation of the risk of non-compliance with antihypertensive treatments in diabetic patients

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Introduction
High blood pressure (HBP) is a public health problem because it is a major cause of global morbidity and mortality. Antihypertensive therapy has evolved significantly in recent years to reduce the number of tablets to improve adherence therapy.
Purpose of our work
The purpose of our work was to estimate the risk of non-compliance with antihypertensive treatments for a population of hypertensive and diabetic patients, by using a validated calculator.
Patients and methods
This is a retrospective study that collects all hypertensive patients hospitalized in our department from December 2017 to January 2018. For the calculation of the risk of nonobservance, we used a validated calculator available online at http://www.comitehta.org/flahs-observance-hta/.
Results
We included 60 hospitalized hypertensive diabetic patients. The average age was 64.87 years with a s.d. of 9.99 years. The sex ratio was 2.1. All patients were diabetic treated with insulin. 43 patients were on both insulin and oral antidiabetic drugs. Hypercholesterolemia was noted in 80% of our patients (48). Coronary heart disease was noted in 20% of our patients (12). 37 patients were suffering from vision disorder: 10 patients are followed for cataract and 17 others are followed for diabetic retinopathy. The average number of tablets taken for HBP was 2.6 with a standard deviation of 0.93. Angiotensin converting enzyme inhibitors and calcium channel blockers are prescribed in respectively 80% and 43.3% of cases. The calculation of the risk of non-compliance concluded that 48.3% of our patients (29) had a high risk of non-compliance, 35% had an intermediate risk and only 17.7% had a low risk of non-compliance. The risk of high nonobservance was noted in 17 women and in 12 men with a significant difference ($P=0.05$). A number of tablets >3 alone is not correlated with a higher risk of non-compliance (Kappa$=0.29$). However, its association with retinopathy increases the risk of non-compliance ($P=0.01$).
Discussion and conclusion
The risk of nonobservance calculator is an easy, accessible and available tool, allowing the optimization of antihypertensive treatment according to the profile of the patients. Its use must be wider in order to better control the High blood pressure.

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EP82

Deep abscess in the diabetic patient

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Introduction
Deep abscess represent infectious emergencies. The aim of our study was to evaluate the clinical, biological, radiological and evolutionary of deep abscess in diabetic patients.
Patients and methods
A prospective descriptive study was conducted over a period of 12 months in 2017, including 52 diabetic patients hospitalized in the University Hospital with a our patients deep abscess.
Results
The average age of 52.4 years, a sex ratio of 2.06 M/F, type 2 diabetes predominant (84.6%), an average age of 7 years, a lack monitoring (53.8%), an average HbA1c of 10.5% and degenerative complications (69.2%). Clinical signs found in our patients were fever (34%), pain in the right upper quadrant (28%), earache (8%), localized pain (10%) and proptosis (14%). We noted that 40% were asymptomatic. Biological assessment achieved found a high CRP (88%) with an average of 47.4 mg/l, leukocytosis (50%), multiple abscesses on ultrasound (85%) with an average size of 7 cm, and infiltration/or collection at tomography (60%).We noted the following locations: liver (19), ocular (12), ORL (5), lung (4), psoas (2), breast (2), one conus medullaris, a tuboovarian, renal (2), mediastinal (2), parietal (1) and brain (1). A bacteriological analysis was performed in 90% of patients, blood culture (35%) and removal of pus (70%). Gram negative bacilli were predominant: *E. coli* (30%), Klebsiella (60%) for hepatic abscesses, pseudomonas aeruginosa (16.6%) of corneal abscess and specificity of *Aspergillus fumigatus* in the case of a complicated pansunisitis of orbital cellulitis. Combination therapy with surgical drainage (59.6%), an injectable antibiotic therapy alone (30.8%), bi or triple therapy (69.2%) with an average duration of 14 days and intensified insulin therapy. The outcome was favorable in 95% of patients. One patient who died in post-operative following a pulmonary embolism.
Conclusion
Our study highlighted the interest to seek a deep abscess before any imbalance with a clinical picture which is sometimes little noisy, to improve patients prognosis, which is overshadowed by the lesions severity and delayed diagnosis.

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EP83

Abscess in the diabetic patient

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Introduction
Hypoglycemia in diabetic patient is susceptible to infection incidence (abscesses). The aim of our study was to evaluate the clinical, biological, radiological and bacteriological abscesses in diabetic patients.
Patients and methods
We conducted a study prospective, including 74 diabetic patients with a confirmed abscess admitted our hospital, from January to December, 2017. Variables studied were epidemiological, clinical, paraclinical and therapeutic. Analysis was done by excel.
Results
Average age our patients were 51 years, a sex ratio of 1.64 M/F. We found average HbA1c of 8.3% and a kenotic decompensation (60.8%). Localizations were: Brain (1), ORL (9), eye (12), lung (4), mediastinal (1), liver (19), psoas (2), breast (2), conus medullaris (1), genitourinary (6) and skin (15). Clinical presentation was polymorphic and insidious on set but corresponded to the site of the abscess for soft tissue infections. Biological assessment found a high CRP (78.2%) and leukocytosis (60%). Identification was based on bacterial blood cultures (40%) and drained fluid analysis (70%). Germs found were: Klebsiella (42.16%), *E.coli* (20.3%), pseudomonas aeruginosa (10.8%), staphylococci and/or streptococci (39%), a specificity of Aspergillus fumigates and of Candida tropicalis. Treatment was medical and surgical, antibiotic susceptibility testing with suitable average duration of 2 weeks and a strict glycemic control. Outcome was favorable in 95% of cases.
Conclusion
The poorly controlled diabetes is a field of immunosuppression favoring infection in various locations. Abscess diabetic patients are often localized in the liver and the eye, with a hight prevalence of Klebsella pneumonia.

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EP84

A case report of MODY 2 treated as type 2 diabetes mellitus in pregnancy

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Introduction
Maturity-onset diabetes of young (MODY) type 2 is caused by mutation of the glucokinase gene. It is characterized by mild fasting hyperglicemia and absence

of vascular complications. It is estimated that the incidence of gestational diabetes is 3%. We aimed to present a pregestational diabetic case with MODY-type 2 in pregnancy.
Case report
A 38-year-old pregnant woman was referred to our clinic for glycemic regulation at 22th week of gestation. She had diagnosis of diabetes mellitus 2 years ago and she was on metformin therapy before pregnancy. Her body mass index was 23.8 kg/m^2 and physical examination findings were normal. Laboratory test results were HbA1c: 7%, fasting serum glucose: 114 mg/dl, C-peptide: 1.85 ng/ml, total cholesterol: 262 mg/dl, triglyceride:138 mg/dl, LDL-cholesterol: 169 mg/dl, Creatinine: 0.76 mg/dl. Her mother and cousin of her mother had diabetes mellitus also. She had two daughters with 23 and 12 years of age. 12-years-old one was being followed in the pediatric polyclinic due to impaired fasting glucose. Because of her family history and BMI $<$ 25 kg/m^2, genetic analysis for MODY was performed. Insulin therapy was started as her glycemic regulation could not be provided with medical nutrition therapy alone. The insulin requirement for glycemic regulation was up to 72 units/day (1.24 U/kg) towards to the end of the pregnancy. No complications were observed in obstetric follow-ups of the patient. At 38th week of gestation, she gave birth to a 3700 g baby by C/S. Genetic analysis demonstrated heterozygous mutation of p.G81S (c.241G>A) compatible with MODY 2 and polymorphism of IVS9c.1253 + 8T $>$ C (rs2908274) associated with 'Type 2 diabetes'. These genetic findings were also determined for newborn baby and 12-years old daughter.

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EP85

Impact of magnesium deficiency on chronic complications of type 2 diabetes

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Introduction
The magnesium deficiency is frequently associated with diabetes mellitus, it is also incriminated in the occurrence of diabetic complications (micro and macrovascular). Our objective was to study the correlation between magnesium deficiency (Mg) and the presence of chronic diabetic complications.
Material and methods
Prospective study that concerned type 2 diabetics (T2D). Our patients were subdivided into 2 groups G1 and G2: G1 including 17 patients with Mg deficiency, G2 including 13 patients with normal Mg status.
Results
G1 and G2 patients had a mean age of 60.4 $\pm$ 7.5 years and 53.1 $\pm$ 11.6 years, respectively. The sex ratio (H/F) was 0.54 in G1 and 1.6 in G2. G1 patients had a more unbalanced T2D than G2 patients. Diabetic retinopathy, diabetic nephropathy and autonomic neuropathy were observed in 37, 30 and 10% of cases, respectively. These complications were more common in G1 subjects, but without a statistically significant difference between the two groups. The prevalence of microalbuminuria was higher in G2 patients compared to G1 (15.3% vs. 6%). Lower extremity arterial disease was found only in G1 with a frequency of 6%. Coronary and cerebrovascular disease were noted more frequently in G1.
Conclusion
Several mechanisms could explain the role of Mg deficiency in the development of chronic complications of T2DM including the increase in oxidative stress resulting from Mg depletion.

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EP86

Severe hypertriglyceridemia in type 1 diabetes accompanied by acute pancreatitis and organomegaly

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Case report
21-year-old female patient visited the emergency department with repeated attacks of vomiting accompanied with continuous non radiating epigastric pain diagnosed as acute pancreatitis. She had three plasmapheresis sessions. She gave history of recurrent similar attacks for the last 5 years with frequent hospitalization she is known diabetic since the age of 15.Hypertensive for 1 year. Menarche at age of 14 with only one cycle. Upon admission, the patient was alert, Weight: 60 kg, height: 164 cm. BMI: 22 pulse: 90 beat/minute blood pressure: 130/70 respiratory rate: 14/min. Temperature: 37°C. Physical examination: eruptive xanthoma on the extensor surface of the forearms and back. Cardiac examination: apex localized in the left fifth space outside MCL, hyper dynamic. Hepatomegaly two fingers below RT costal, normal fundus, normal neurological examination Breast: Tanner 3, Pubic hair: Tanner 4 Laboratory investigations; RBS 375 mg/dl HBA1C: 14.7%, ABG (PH: 7.38 HCO3: 26 Mm/l SaO2 98.0%) CBC HB;11.6 g/dl, TLC: 5.800/ul PLT:245,000/ul/CRP: 132 mg/dl/Chol: 464 mg/dl, LDL: 257 mg/dl, HDL: 25 mg/dl, TG: 9068 mg/dl amylase: 1120 U/l, Lipase: 370 U/l/Na: 141 mEq/l, K: 3.8 mEq/l, Urea: 34 mg/dl Creatinine: 5 mg/dl, 24 h. Urinary PTN: 1.146 g. ALT: 17 IU/l, AST: 19IU/l,Bil T: 0.9 mg/dl, albumin: 4 g/dl FSH: 0.1, LH:0.5, Estradiol:5, TSH:1.7, FT4:1, ACTH:12, Cortisol AM:8, GH:0.1 ng/ml. Abdominopelvic sonar showed: Enlarged Bright hepatomegaly 16 cms, Mild splenomegaly. Diffuse enlarged pancreas of hypo echoic pattern, picture suggestive of acute pancreatitis. Enlarged swollen kidneys (RT kidney 154*48 mm, LT kidney 152*75 mm.) CT abdomen with contrast: diffusely enlarged pancreatic head. X-ray both arms: Bilateral distal humorous multiloculate bubbly lesion with sclerotic margin. Echocardiography: Concentric LT ventricular hypertrophy. MRI brain (Bulky pituitary gland showing a focal central bulge (0.4 $\times$ 1 $\times$ 0.7). Renal biopsy: Minimal change glomerulonephritis. After three plasmapheresis sessions, Intravenous insulin a marked reduction in triglyceride/total cholesterol levels was observed. CHOL 334 mg/dl, LDL 190 mg/dl, HDL 48 mg/dl, TG 880 mg/dl. She was discharged on dietary, lifestyle modifications and fenofibrates 4 month later she came for follow up Marked improvement of her xanthomata, regular cycles, TG 627mg/dl, HbA1c:8.9, normal pituitary imaging, no organomegaly.
Conclusion
Patients with severe hypertricylcerideamia require fast and effective lowering of TG levels in order to reverse the lipotoxic effect on different organs

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EP87

Diabetic ketoacidosis and acute pancreatitis associated with antipsychotic drugs: report of a case

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Introduction
Diabetic ketoacidosis (DKA) is a feature of type 1 diabetes mellitus, but it can develop in people with type 2 diabetes (T2DM) in the presence of precipitating factors. Antipsychotics have been associated with pancreatitis without DKA or hyperglycemia or acidosis with no evidence of pancreatitis. To our knowledge, there are few reports of patients who developed pancreatitis and DKA during treatment with antipsychotis. We present a case of a patient who developed such life-threatening conditions while on antipsychotics.
Clinical case
A 53-years-old Caucasian woman (BMI 32.7 kg/m^2) was transferred to our Unit from the ED where she was admitted for dyspnea and abdominal pain. She had T2DM, managed with diet, and bipolar disorder treated with mood stabilizers and antipsychotics (valproic acid, haloperidol, quetiapine). Initial lab results revealed hyperglycemia (446 mg/dl; HbA1c 118 mmol/mol) and metabolic acidosis (pH 7.0; HCO3- 5.3 mmol/l; 3-beta-hydroxy-butyrate $>$ 3 mmol/l; BEE $-$25 mmol/l). Patient received i.v. fluid and insulin therapy until DKA resolution, but clinical course was complicated by acute pancreatitis (amylase 550 U/l; lipase 1574 U/l). Abdomen CT showed moderate edematous acute pancreatitis, with no evidence of stones or bile duct dilatation. On admission and during the early phase of acute pancreatitis, triglycerides were modestly increased (365 mg/dl). Supportive care with i.v. fluids, bowel rest and pain control were mainstays of therapy. The patient became medically stable after 15 days of hospitalization. Before withdrawal insulin, metformin was introduced with maintenance of satisfactory glycemia (fasting 122 mg/dl; post-prandial 124 mg/dl). Antipsychotic medications were reviewed after psychiatric consultation.
Discussion
We present a case of a T2DM patient who developed pancreatitis and life-threatening DKA while receiving antipsychotics, that may be the common denominator linking DKA and acute pancreatitis though the exact mechanisms responsible remain to be identified. As far as DKA is concerned, antipsychotics may have an isolated toxic effect on beta-cell resulting in relative

hypoinsulinemia and hyperglucagonemia. Marked hypertriglyceridemia can trigger acute pancreatitis, but triglyceridemia were only moderately increased in our case. This suggest that in our patient pancreatitis may be the result of drug-mediated acinar-cell damage or idiosyncratic drug reaction. In summary, physicians should be aware of the possibility of life-threatening adverse effects in T2DM patients on antipsychotic treatment especially when in combination with mood stabilizers. These subjects should undergo careful monitoring as they may have inappropriate assessment of signs and symptoms.

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EP88

Diabetic ketoacidosis, hypertriglyceridemia and acute pancreatitis- a case report

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Diabetic ketoacidosis (DKA) is a state of absolute or relative insulin deficiency characterized by hyperglycemia, metabolic acidosis and ketosis and occurs mainly in type 1 diabetes mellitus (DM). While enhanced lipolysis and inhibition of lipoprotein lipase in DKA lead to typically not severe elevation of triglyceride (TG) level, extreme hypertriglyceridemia (HTG) is rarely seen. If complicated with acute pancreatitis (AP), DKA and HTG form a scarcely reported triad, controversial regarding pathophysiology and possible sequence of events. We report a case of a 35-years-old obese male, non-smoker, admitted to the hospital through the emergency department because of a worsening, sharp pain in upper abdomen associated with high fever, anorexia, nausea and vomiting. His past medical history included dyslipidemia diagnozed 2 years ago (shortly on statins) and cholecystectomy 9 years ago. He denied any alcohol consumption. On physical examination, he was concious, dehydrated, dyspneic and normotensive, with mildly tender abdomen in epigastric region. Laboratory findings revealed blood glucose of 24.6 mmol/l with metabolic acidosis and positive ketones in urine. His serum was milky and turbid, which suggested severe HTG: measured TG level was 110 mmol/l. Serum amilase and lipase levels were 878 and 1862 IU/I respectively. A contrast-enhanced computed tomography of the abdomen confirmed the diagnosis of AP. Upon admission, DKA and AP were successfully treated by insulin infusion, intravenous hydratation, potassium supplementation and analgesics. Additional analysis showed normal level of C-peptide, glycated hemoglobin (HbA1c) of 13.4% and negative immunology for type 1 DM which supported the diagnosis of DKA as initial manifestation of type 2 DM (T2DM). The reported case of DKA in adult with previously undiagnosed T2DM accompanied with severe HTG and AP demonstrates a significance of multidisciplinary approach concerning a challenging prompt diagnosis, treatment modalities and consequent follow-up after hospital discharge.

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EP89

Implications of dietary omega-3 fatty acid supplementationon oxidative damage and inflammatory response in type 2 diabetic depressive patients

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The prevalence of depressive symptoms in patients suffering from type 2 diabetes is commonly acknowledged. Even mild depression is recognized as clinically relevant for the general health outcomes in this vulnerable patient group. Research in this area has been focused on biochemical markers reflecting common pathological processes of insulin resistance, inflammation and oxidative damage, all being assumed to be interconnected in both diabetes and depression. Most of the studies revealed the massive inference of oxidative stress in diabetes pathogenesis by the alteration in enzymatic systems (catalase, superoxide dismutase), lipid peroxidation, impaired glutathione metabolism and decreased vitamin C and lipoic acid levels. Reactive oxygen species cause damage to lipids, proteins and DNA when in excess, and can ultimately result in cell death, playing a role in the pathophysiology of diabetes mellitus, cardiovascular disease, cancer and a number of psychiatric disorders, including depression. Oxidative stress is a candidate pathway that may link depression to physiological changes. Also, a hypothesis on the involvement of inflammatory as well as oxidative stress pathways in the pathogenesis of depression has received much attention. Association between depression and oxidative damage due to both increased reactive oxygen species production and decreased antioxidant capacity has been clearly demonstrated, suggesting that oxidative stress might provide a plausible biochemical link between depression and unfavorable health outcomes. The most likely generator of oxidative stress in depression is considered to be a chronic, low-grade inflammation resulting from activation of cellular immunity able to induce an immune-mediated damage to the cells. In the present clinical study, we aimed to assess changes that occurred during a period of 6 months, consequent to the administration of polyunsaturated fatty acid supplements (300 mg of omega-3 fatty acids). Biomarkers of oxidative stress and inflammation were evaluated in three different groups of patients: non-diabetic but depressive patients; diabetic, but non-depressive patients; and finally, in diabetic-depressive patients. Results were corroborated with cortisol and serotonin levels, in order to provide a clear conclusion on the molecular homeostasis modulation effects of omega-3 fatty acids. The unequivocally obtained regulatory effect of omega-3 fatty acids can be explained by the fact that it stabilizes cell membranes, participates constitutively in their structure, normalizing membranes fluidity and improving cell membranes' ability to counteract oxidative stress.

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EP90

Psychosis because of alcohol abstinence in a diabetic subject

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Introduction
Although psychiatric manifestations in the form of delirium, confusional states, and psychosis have been commonly reported in relation to hypoglycemia, association of hyperglycemia with psychiatric manifestations has been less commonly reported. Acute hyperglycemia is known to alter mood state and impairs cognitive performance in patients with diabetes mellitus. However, association of acute psychosis (in the absence of cognitive disturbances) with hyperglycemia has not been reported. It is generally accepted that alcohol-related psychosis remits with abstinence.
Case report
We report the case of a male 67 years old diagnosed with diabetes mellitus (DM) 3 years ago, treated with combined hypoglycemic oral medications, which has been discontinued for some days. He consumed high quantities of alcohol for many years, but he had stopped drinking for two days. He presented in emergency unit with these complaints: Vomiting, epigastric pain, Polyuric-polydipsic syndrome, fatigue, agitation. Familiar history negative. Objectiv examination: conscious, active position, low turgor skin, dry tongue, rhythmic heart rate, TA 110/60 mmHg, Fc 88/1 min. lungs normal, lower limbs neither edemas nor wounds. Blood biochemistry: glycemia 615 mg/dl, urea 82 mg/dl, creatinine 3.7 mg/dl, AST 49U/L(0–35), AlT 23 U/L(0–45), LDH 340 U/l (0.3–1.2),total protein 5.9 g/dl (6.2–8.3), troponin 0.283 ng/ml. WBC 5100, Granulocyte 80.2%, lymphocytes and monocytes normal. RBC 3.14 million/mm^3, HGB 10.9, PLT 187/mm^3, MCV micron/m^3 100 (80–97), urine analyses: negative acetone, albumin 2.64 g/leukocyte filled areas, 4–5 erythrocytes/field. Imagery examination:Abdominal ultrasonography, hepatosteatosis, liver with large dimension 158 mm, rough echo structure, portal vein 11 mm, pancreas normal.without peritoneal liquid. According to surgeon consultation, the patient was without acute surgical problems. He was treated with Insulin, fluids, electrolytes,thiamine, antibiotics.The next day: The general condition was better but he had visual hallucinations and he wanted to leave the hospital during the night. Psychiatrist Consultation: Psychotic Symptoms caused by alcohol abstinence. After starting of the psychiatrist treatment with Librium 10 mg 3x1 tb, haloperidol 2×10 drops, he was feeling better.
Conclusion
Psychosis in a diabetic person (alcohol user) with hyperglycemia, can be caused by stopping drinking for only some days. Every physician must be aware about this situation to diagnose it early, and to prevent sad results.

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Environment, Society and Governance

EP91

Selfie driven thyroid disease leads (SET): a study on a unique phenomenon from Surgical Endocrinology Department

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Introduction
Taking a photograph of self alone or with a group called Selfie, has become modern day rage with spurt in smart phone technology. It has catapulted from a hobby in to psychiatric ailment, especially amongst teens and young adults. Though, it is considered as a psychiatric aberration keeping them aloof from social interactions, we observed an inadvertent advantage in this habit. In this context, we present some intriguing findings through this study.
Material and methods
This retrospective study was based on compilation of 6 cases from endocrine surgery outpatient and inpatient database collected over 2 years period. The inclusion criteria are – the chief complaint (CC) was noted only after watching the selfie picture and not otherwise; the patient is obsessive of taking frequent selfie photographs and/ or uploads their pictures frequently in social media ($\geq$3 pictures/day); the CC lead them to consult physician; the picture was captured by oneself or other person who was part of that image; the CC lead to definitive diagnosis of thyroid disease requiring treatment. All other clinical, investigative and treatment (medical and surgical) were studied.
Results
In all we had 6/5520 (0.0011%) cases meeting the above criteria. CC and later confirmed in pictures were three cases of Grave's disease associated ophthalmopathic exophthalmos, two cases of goiter and one case of facial puffiness (myxoedema related). All these CC helped in diagnosing Graves' disease (3), Nodular goiter (2) and hypothyroidism confirmed by appropriate investigations. 4 cases underwent thyroidectomy, two cases took conservative medical treatment.
Conclusions
Though selfie is considered as a modern day life style induced psychiatric disease, sometimes it can help in picking up endocrine diseases in earlier stages.
Keywords: Thyroid; Exophthalmos; Goiter; Selfie, Endocrine
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Interdisciplinary Endocrinology

EP92

FGF21 levels in patients with breast cancer

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Aim
FGF-21, is a member of the FGF family that is involved in biological processes such as embryonic development, cellular growth, morphogenesis, tissue repair, tumor growth and invasion, with mitogenic and cellular vital activity activity in the cytogenetic localization of 19q13.33. Breast cancer is the fatal disease most commonly seen in women and increasing in frequency and the relationship between hormones secreted from adipose tissue and some cancers has been shown in recent studies. Our aim in this study is to measure FGF21 levels in breast cancer patients and show their association with breast cancer.
Method
39 patients with newly diagnosed breast cancer and 39 healthy subjects as control group were participated in the study. An extra tube blood sample was taken during the patient's routine blood test and FGF-21 was studied by ELISA method from serum samples.
Results
The demographic and laboratory data of the newly diagnosed breast cancer patient group and the control group were compared. The control group consisted of 39 participants with a mean age of 52.49 $\pm$ 7.02 years. In the patient group, 39 participants with a mean age of 52.15 $\pm$ 6.21 years were included in the study. In the control group, average FGF21 measurement was 121.35 $\pm$ 88.4 pg/ml, while FGF21 measurement in the patient group was 171 $\pm$ 117.45 pg/ml and a significant difference was detected (*P*: 0.036).
Conclusion
It has been thought that FGF21 has significant and positive effects on glucose, lipid and energy metabolism as well as slowing effects on growth in cancer cells and may be used later as a biological marker for breast cancer.
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EP93

Pharmacological chaperones for rescue of the mutant AVPR2s

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Using pharmacological chaperones is one of the most common area to rescue trapped proteins from Endoplasmic reticulum (ER) or Golgi apparatus as therapeutic targets in research of some endocrine disorders. Diabetes insipidus is one of these disorders and AVPR2 is seen mostly mutated in hereditary type of the disorder. As proteins go through a journey from ribosome till the place where they function at, AVPR2 also tracks the same way as a G-protein coupled receptor. A mutation in AVPR2 could effect three dimensional functionally active structure of the protein and it could be trapped in ER or Golgi apparatus. Consequently, its cell surface expression, which primarly locates at the basolateral membrane of principal cells in the collecting duct, could decrease which shows its affects on the syptoms. As a therapeutic agent, SR121463A and SR49059 are commonly used for research the rescue potential of mutant AVPR2s. We aimed to show the rescue potential of SR121463A and SR49059 as a pharmacological chaperones in treated AVPR2 mutants (G12E, R68W, ΔR67_G69/G107W, V88M, R106C, V162A, T273M). These mutants were previously described and functionally analysed by our group. After treatment with SR121463A and SR49059, cell surface expression analyses were done for mutants. This work was funded by The Scientific and Technological Research Council of Turkey (SBAG Project No: 216S304). As a result, these pharmacological chaperones showed that they has a rescue potential at different levels according to the mutation. Some mutations have severe symptoms and also they showed loss of function but we could show the rescue of these some mutants using with SR121463A and SR49059. In conclusion, as a therapeutic target, SR121463A and SR49059 could be used to rescue of some mutated AVPR2s *in vitro* and many of these kind of targets are mainly used. To get a more clear view, we will perform cAMP accumulations assay and cell imaging analysis for these mutants using with SR121463A and SR49059. In our opinion, these kind of *in vitro* studies will be helpful to use of these pharmacological chaperones *in vivo* and shed light to the future studies. Especially for the disorders which have severe symptoms, *in vitro* and *in vivo* studies have an importance to reduce the severeness of the symptoms.
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EP94

Tolvaptan; OPC-41 061, Mozavaptan; OPC-31 260, OPC-21 268 as pharmacological chaperones to rescue of mutant AVPR2s

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Nefrojenic Diabetes insipidus is one of the typical conformational disorders result from protein misfolding and degredation or aggregation due to the mutations in AVPR2. The patients of nephrogenic Diabetes insipidus have difficulty in concentrate of urine and because of this, they have polyuria, hypoosmolar urine and hypernatremia in variable levels. To make them relieved, many treatment strategies have been studying and using dDAVP nasally is one of these strategies. Another treatment approach on this type of conformational disease is *in vitro* treatment of mutant AVPR2s with pharmacological chaperones (PCs). PCs are small molecules that bind to misfolded proteins and stabilize them and rescue these mutated proteins from quality control system of Endoplasmic reticulum. In this study, Tolvaptan; OPC-41 061, Mozavaptan; OPC-31 260 and OPC-21 268

were selected as pharmacological chaperones for treatment of previously identified and functionally analyzed mutations (R68W, DR67_G69/G107W and T273M) by our group. As a functional analysis, we performed cell surface ELISA after the treatment of mutant AVPR2s with OPC-41 061, OPC-31 260 and OPC-21 268. Our study was supported by The Scientific and Technological Research Council of Turkey (SBAG Project number 216S304). According to the ELISA results, some mutant AVPR2s could be rescued after the treatment with OPC-41 061, OPC-31 260 and OPC-21 268, separately. In conclusion, we think that using pharmacological chaperones *in vitro* has an importance on developing treatment strategies for these kind of conformational disorders. In the future, we will perform more functional analysis experiments on these mutants after the treatment with OPC-41 061, OPC-31 260 and OPC-21 268, separately. Consequently, all these analysis will make us to understand the precise affect of OPC-41 061, OPC-31 260 and OPC-21 268 *in vitro*.

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EP95

A case with autoimmune polyglanduler syndrome type 3A

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Introduction
Autoimmune polyendocrine syndromes (APS) are rare endocrinopathies characterized by the coexistence of at least two glandular autoimmune diseases. APS comprise a wide spectrum of autoimmune disorders and are divided into a very rare juvenile (APS type 1) and a more common adult type with (APS 2) or without adrenal failure (APS 3). We present a patient with polyglanduler syndrome type 3a.
Case report
A 39-years-old female patient was presented to our emergency department with the complaints of nausea, vomiting and urinary incontinence. She was consulted to our endocrinology clinic with the diagnosis of diabetic ketoacidosis. In her physical examination, webbed neck, shortness of height (145 cm), low hairline at the back of the neck, exophthalmos and genu valgum was determined. In her past medical history, she had received intermittent hormone replacement therapy because of primary amenorrhea and she had been diagnosed with diabetes mellitus 2 years ago and she was using oral antidiabetic drugs also added insulin treatment for the last 6 months. The patient was admitted to our clinic and underwent insülin infusion and fluid replacement therapy.Laboratory testresults as follows glucose: 114 mg/dl, HBA1C: 11,8%, TSH >0.005 uIU/ml, FT4: 0.98 ng/dl, FT3: 4.8 pg/ml, anti-TPO: 600 IU/ml, anti TG: 341.2 IU/ml (0–115), FSH: 36 mIU/ml, LH: 15 mIU/ml, E2: <5 pg/ml, Cortisol: 18.96 ug/dl. The patient's anti GAD and ICA antibodies were positive and the patient was diagnosed as Type 1 diabetes mellitus. The intensive insülin treatment was started after resolution of diabetic ketoacidosis. The thyroid stimulated antibody was positive and the scintigraphy and ultrasound was consistent with the graves. The genetic test for hypergonadotropic hypogonadism was consistent with Turner's syndrom(46X DEL (X) Q13). ANA, celiac antibody, anti-parietal antibody and the other autoimmun antibodies which screening were negatively determined.
Discussion
The third type has been described in adults that, contrary to types 1 and 2, does not involve the adrenal cortex. No clinical differences between types 2 and 3 have been described except the absence of adrenal failure. APS-3A includes autoimmune endocrine diseases autoimmune thyroid disease, type 1 diabetes mellitus, lymphocytic hypophysitis, premature ovarian failure, and Hirata's disease. It is concluded that patients with a single autoimmune component of polyendocrine syndrome should be screened to exclude other autoimmune endocrine disorders.

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EP96

Cardiotoxicity from glycyrrhizic acid inhibition of 11-beta steroid dehydrogenase

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Ingestion of excessive amounts of liquorice may cause significant electrolyte imbalances due to a mimicking of mineralocorticoid excess. A 70-year-old female attended hospital with palpitations and was found to have hypokalaemia. She was documented to have multiple supraventricular ectopic beats coinciding with her feeling of palpitations, This was precipitated by toxic consumption of liquorice, more than 2 kg in 72 h, to celebrate her 70th birthday. All abnormalities resolved with abstinence from further birthday liquorice. Mineralocorticoids and corticosteroids are structurally similar and bind equally to the Minrealocorticoid Receptor (MR). It is the selective presence of isoform 2 of 11beta-hydroxysteroid dehydrogenase (11BHSD) that downregulates the effect of cortisol in the tissues mentioned above. This enzyme utilizes NAD to oxidize cortisol to the inactive cortisone to prevent MR activation. Isoform 1 of this enzyme is present in all metabolic tissues to conversely reduce cortisone to cortisol to activate Glucocorticoid Receptors. Therefore, the placement and function of 11BHSD is critical to preventing an apparent mineralocorticoid excess from the unopposed effect of cortisol on a non-selective MR. Liquorice root (Glycyrrhiza glabra) contains glycyrrhizic acid (GZA), this molecule directly inhibits type 2 11BHSD. Acceptable safe dosage is 0.2 mg/kg with toxic doses beginning at consumption greater than 2 mg/kg. Given that liquorice contains 0.2% GZA by mass, a 60 kg adult would therefore exceed safety at 6g and reach toxicity at 60 g of liquorice per day. Our patient's intake therefore exceeded this by a factor of 11. Hypokalaemia has long been associated with an increase in cardiac conduction abnormalities. The resultant hypokalaemia from upregulating the aforementioned pumps then has three major cardiotoxic effects in that it inhibits outward potassium currents in ventricular tissue, it inhibits the cardiac $Na+-K+$ pump, and the resting membrane potential is elevated with increased threshold for depolarization and hyperpolarized, this generally slows effective wave conduction. The combination of these three effects therefore facilitates re-entry rhythms with resultant tachyarrhythmias. Reports of these are not new, but they are usually in extremis. A case in Turkey linked the ingestion of liquorice to an episode of ventricular fibrillation in a patient with Brugada syndrome. Similarly, a patient from Oman developed recurrent polymorphic ventricular tachycardia episodes however, she was morbidly obese. Our patient was unique in having a structurally normal heart without cardiac risk factors and her rhythm returned to its baseline without intervention, thus, demonstrating the early stages of liquorice-induced cardiotoxicity.

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EP97

Stein leventhal syndrome: a report of two cases

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Introduction
The polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women. Its clinical manifestations are characterized by infertility, hirsutism and obesity. We report two cases of PCOS but with different signs revelations.
Observation 1
23 year old patient presenting with metabolic syndrome, with dysmenorrhea, after investigation, diagnosis of type two diabetes with PCOS.
Observation 2
Patient aged 35 years old who consults for infertility that lasts for 5 years with obesity and hirsutism, diagnosis PCOS was diagnosed according to different criteria clinico' radiologiques.
Results
For both our patients the care first focus was weight control, changes in eating habits, promote physical activity. Introduction of an oral antidiabetic (metformin) for both our patients and correction of cardiovascular risk factors.
Discussion
Most published studies confirm that metformin improves insulin sensitivity and reduces hyperinsulinemia in PCOS in a similar manner to what is known for patients with type 2 diabetes. In addition, the reduction of the insulin is associated to hormonal changes: increase of SHBG, decrease in circulating levels of LH and hyperandrogenism, often with improvement of ovulation.
Conclusion
The polycystic ovary syndrome is a common condition affecting nearly 12% of women of childbearing age. It is characterized by an increase in plasma testosterone and LH, and insulin resistance, mainly in anovulation, diet and lifestyle rules and metformin, can give satisfactory results.

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EP98

Diabetes mellitus reveals malignant vaterian ampulloma

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Introduction
Diabetes is a risk factor for pancreatic cancer and recent studies confirm this relationship. We report the case of a patient in whom an inaugural diabetes mellitus revealed a malignant vaterian ampuloma.
Observation
A 56-year-old woman with a family history of type 2 diabetes consults for suspicion of type 2 diabetes, polydipsic syndrome, and all-day hyperglycaemia greater than 2 g/dl. During the interrogation, there is a loss of appetite, a significant weight loss without quantification, a cutaneous-mucous sub-jaundice, pruritus and clinical cholestasis syndrome. Presence of a biological cholestasis syndrome with vaterian ampulloma at bili-MRI, an adenocarcinoma was confirmed in the pathological study. Insulin therapy has been initiated for the treatment of diabetes mellitus and surgical treatment such as duodeno-pancreatectomy due to the invasive nature of the tumor, currently the patient is post-surgery stable but very unbalanced in terms of glycemic control.
Conclusion
The link between diabetes and pancreatic cancer is well known, but the mechanisms of this association remain to be clarified. Between type 2 diabetes associated with pancreatic neoplasia or paraneoplastic diabetes, hence the importance of monitoring newly diagnosed diabetics.

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EP99

Where is the hitch in our interdisciplinary approach? Perceptions of health care providers towards the challenges at diabetes management clinics in Oman

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Background
The diabetes management clinics in primary health care centres in Oman aim to provide interdisciplinary diabetes management for their patients. The inter-disciplinary management is proved in the literature to have successful outcomes and help the patients to reach their glycemic control fast and safe. Therefore the diabetes management in Oman follows national guidelines, which are based on IDF and AACE guidelines and support the interdisciplinary approach. Despite the presence of guidelines and interdisciplinary team, the diabetic clinics still face several challenges that can affect the health care providers interdisciplinary approach and the diabetic patients' glycemic goal and cause serious implications.
Materials and methods
A study was conducted in five purposely-selected health care centres in Muscat the capital of Oman to explore the present challenges and their implications on the diabetic service provision. The methodology used was non-participant observations and interviews with members of the team that includes: physician, nurse, dietician, health educator, pharmacist, assistant pharmacist, psychologist and medical orderly.
Results
The results disclosed several challenges related to diabetes management clinic at public primary health care centres. The challenges were related to many factors including health care providers' shortage and communication, health providers' interests, knowledge and skills, interdisciplinary service provision, cultural believes and traditions in the community, in addition to diabetes and health awareness in the country.
Conclusion
The study disclosed perceptions of care providers towards challenges related to diabetes management clinics in three different settings in public primary care and within two contexts: health care centre and community. The study identified the findings in the frames of the providers' tasks and roles during service provision and addressed them at different levels with a lot of involvements, shared responsibilities and implications.

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Pituitary and Neuroendocrinology

EP100

Characteristics of clinical and morphological features of functioning and nonfunctioning pituitary adenomasand disorders commonly associated with them

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Background
The prevalence of pituitary adenomas (PAs) is increasing as the development of imaging techniques. The objective of this study is to assess the clinical and morphological features of non-functioning, prolactin, and grown-hormone secreting pituitary adenomas and to analyze the accompanying diseases of each condition.
Methods
A retrospective analysis of the clinical records of patients with non-functioning (NFPA), prolactin (PRL+) or grown hormone (GH+) secreting adenoma was performed. A total of 194 patients who attended Vilnius University Santaros Clinic's in the year of 2016 were analyzed.
Results
The distribution of each pituitary adenoma subtype was prolactin-secreting adenomas occupying 45.9% of the total subjects. The study founds that between all PAs, men have significantly larger tumors (average 23.46 mm) than women (average 11.84 mm). Most patients complain of one symptom related to their diagnosis, patients who complain of three and more symptoms tend to have bigger tumors (12.27 mm – average size in one symptom group, 16.87 mm – in three symptoms group), however, there is no significant correlation between the higher number of symptoms and tumor size. Headaches were the most common symptom among NFPA patients (36.5%), menstrual dysfunction in females was among PRL+ group (36.4%) while enlargement of hands and feets were in GH+ group (48.7%). Younger patients were more often diagnosed with prolactin-secreting adenomas (average 39 years old), nonfunctioning and GH secreting adenomas are usually diagnosed within 49–51 years old patients. Thyroid conditions (hypothyroidism, hyperthyroidism, goiter, thyroid nodules and cancer) accompanied 49% of all patients diagnosed with PA's. Statistically significant correlation was between those two disorders was found in GH secreting group, where 81% of patients had had thyroid conditions.
Conclusion
Male patients tend to have significantly larger pituitary tumors than female. Patients with prolactin-secreting pituitary adenomas are more likely to be diagnosed at a younger age compared with patients with nonfunctioning and GH secreting adenomas. There is a correlation between GH secreting adenomas and thyroid diseases.

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EP101

Prolactinoma management: factors that might predict remission of the disease after 12 months of treatment

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Background
Dopamine agonists (DAs) are the primary treatment for both microprolactinomas and macroprolactinomas. Two medications are FDA approved for the medical treatment of prolactinomas: cabergoline and bromocriptine. Although bromocriptine is deemed a secondary option after cabergoline, its lower cost may be a consideration for some patients. The purpose of this study is to analyze patients treated with different DAs during 12 months period and to identify the unchangeable factors that might predict the remission.
Methods
We retrospectively evaluated 89 patients with the diagnosis of prolactinoma who had been treated with dopamine agonists at Vilnius University Santaros Clinics in the year of 2016. The patients were divided into two groups, according to whether biochemical remission was achieved after 12 months of treatment, or not, and the factors that might predict possible remission were analyzed. Patients, treated with both drugs: cabergoline and bromocriptine or with surgery during 12 months period were excluded.
Results
Sixty-six patients (52 women and 14 men) with a mean age of 19–76 years were studied. 44 patients (66.7%) were treated with bromocriptine, while 22 (33.3%) with cabergoline. 46 patients (69.7%) achieved remission after 12 months of treatment while 20 patients (30.3%) did not. 75% of patients used bromocriptine

in a group where remission was not achieved while in the remission group bromocriptine was used for 56.5% of patients. Patients who achieved remission were younger: on average 38.5 years old, while other 41.1 years old, also the initial prolactin level was 8.82 time lower in the remission group.
Conclusion
Although more patients who were treated with cabergoline achieved a positive outcome, it is not statistically significant that cabergoline increases the chance of remission. Possible unchangeable factors that might predict the positive outcomes like the age, a smaller size of the tumor or a lover prolactin level before starting the treatment are not statistically significant either.

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EP102

A differentiated approach to the treatment of pituitary apoplexy

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Introduction
The risk of pituitary apoplexy (PApopl) is up to 9.5%. In 80% of cases, it is the first manifestation of the disease.
Material and methods
The study included 94 PApopl from 1 day up to 9 years. Conservative treatment was performed in 37 cases, and 59 were operated on including 14 giant posthemorrhagic cysts. The probability of resorption – it is possible in 85%, instead of cysts (the probability of resorption of $\sim$ 15%). After 3 months, for PApopl, resorption of the tumor is sharply reduced. The use of Dexamethasone in the treatment shows an important role: slightly increases the probability of resorption and significantly increased the probability of visual oculomotor improvement. Regression hypopituitarism was shown in 87.5% of cases, and it was shown in 17.3% of cases without Dexamethasone. Most of the tumors did not show aggressive growth. Mutation p53 was not found. Only half of the observations identified receptors for epidermal growth factor (EGFR). In almost all cases revealed the expression of Cyclin D1, but the presence of mitosis in tumor cells revealed only a quarter of them. The level of Ki-67 did not exceed 5% in most cases. Quite a separate group of tumors should be considered a tumor with giant posthemorrhagic cysts. This is actually a separate disease. Treatment of such patients is associated with an extremely high risk of complications, and mortality reaches 30%. The most effective method of treatment was transsphenoidal endoscopic cyst evacuation followed by prolonged drainage into sphenoid sinus, in cases without intraoperative CSF-leak.
Conclusion
In contrast to the conventional view, when the most PApopl need for urgent removal, we offer a differentiated approach to the treatment choice depended on the size and radiological characteristics of the tumor and the dynamics of the patient condition during the conservative therapy.

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EP103

Unusual association: turner syndrome and anterior pituitary insufficiency in 6 cases

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Introduction
Turner syndrome (ST) affects 1/2500–1/4000 of female births, its association with congenital malformations is traditional, however the coexistence of hypopituitarism is exceptional. In this context, we report 6 patients; including 3 belonging to the same family and in whom the association of anterior pituitary insufficiency (IAH) to a ST was confirmed.
Results
The average age of our patients was 17.2 years (11–31). The ST was selected for dysmorphic syndrome with impuberism in sporadic cases ($n=3$) and familial cases ($n=3$), except for the fourth sister who presented spontaneous puberty with integrity of the pituitary axes with the presence of an X ring chromosome. Somatotropic deficiency (peak GH <10 ug/l) and corticotropic deficiency (cortisol: average 65 ng/ml and ACTH: average 4 pg/ml) were confirmed in all sporadic cases while the gonadotropic and thyrotropic axes were spared. On the contrary; in familial cases they were consistently affected (FSH: mean 1.1 mU/ml, LH: mean 2 mU/ml, E2 <9 pg/ml, FT4: average 4.2 pmol/l, TSH: average 1.3 mU/l) with integrity of the corticotropic axis. MRI showed pituitary hypoplasia in all familial cases and pituitary stalk interruption syndrome in only one sporadic case. The karyotype showed a monosomy in 3 cases and a mosaic ST in the 3 remaining cases, including one case with abnormal X chromosome structure. No correlation was found between the chromosome formula and the anterior pituitary involvement.
Discussion
We report the largest serie concerning the association between IAH and ST: 6 cases out of 11 in the literature. Co-segregation of congenital IAH with pituitary hypoplasia and X chromosome aberrations could imply a biomolecular anomaly of transcription factors responsible for the differentiation and development of pituitary cells such as: PROP1, POUF1, Hesx1, Lhx3, Lhx4, and Ptx2.
Conclusion
The aetiopathogenic link between X chromosome abnormalities and the occurrence of AHI remains unclear; the progress of molecular biology may clarify the interrelation between transcription factors and sex chromosome segregation abnormalities.

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EP104

Evaluation of differential diagnosis and treatment stages of TSH-secreting pituitary microadenoma which responding to cabergoline therapy

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Introduction
High thyroid hormone levels with unsupressed TSH (atypical hyperthyroxinemia) is one of the difficult endocrinologic conditions. When the conditions leading to euthyroid hyperthyoxinism are excluded, TSH secreting pituitary adenomas (TSHoma) and thyroid hormone resistance beta syndrome (THRB) lead to this picture as rare diseases. This report aims to evaluate the diagnostic and therapeutic stages in the case of TSH-secreting pituitary microadenoma which response to cabergoline treatment.
Case
A 49-year-old male patient was evaluated three years ago for palpitations and sweating. TSH, fT3 and fT4 were found 1.0 μIU/ml (0.350–4.940), 5.2 pg/ml (1.71–3.71) and 1.84 ng/dl (0.70–1.48) respectevely. Patient subsequently losted from the follow-up. Because of the increase in complaints has been reevaluated two months ago and similar findings were found in the tests. Pituitary MRI showed a pituitary adenoma on the left side and 7×4 mm in-size. Atrial fibrillation was present in the clinic, SHBG level was 62 nmol/l (10–57). In the TRH stimulation test, TSH levels were 1.598, 5.43, 6.702, 6.081, 5.521 (considered non-diagnostic). Alpha subunit level was 1.49 ng/ml ($\leq$ 0.5). Cabergoline treatment has been started to the patient because he has not tolerated short-acting sandostatin due to diarrhea. Genetic test result was negative for THRbeta. TSH levels were decreased from 1.39 to 0.86 and fT4 levels were decreased from 1.97 to 1.67. The patient's complaints improved and then after make sure diagnosis of TSHoma he was referred to the neurosurgery.
Conclusion
In patients with atypical hyperthyroxinemia, a very good clinical evaluation should be performed for differential diagnosis between TSHoma and THRB. Negative family history/screening, high alpha subunit level, 5-fold increase in TSH after TRH stimulation, adenoma on MRI are features of TSH-secreting adenoma. However, hypophyseal hyperplasia can be seen in THRB, heterogeneity in clinical findings, genetic testing can not always be done or result is negative in 10% of patients with THRB, makes the differential diagnosis problematic. In patients diagnosed with TSHoma, the pathologic condition is often macroadenoma, but occasionally also microadenoma may occur. Surgical treatment is the main treatment option and long-acting somatostatin analogues are used effectively in patients who can not undergo surgery or who are not cured and for pre-surgery in some patients. The effect of cabergoline is more limited. However, it can be seen that if there are microadenomas and the clinical findings are milder, such as in our case, cabergoline may be considered a suitable option.

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EP105

Case presentation: Double non-functioning pituitary adenomas

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Background
Pituitary adenomas are usually benign epithelial tumors and they are the most common cause of sellar masses from the third decade on, accounting for up to 10% of all intracranial neoplasms. Pituitary adenomas typically present with neurologic symptoms, clinical findings of hormonal abnormalities or as an incidental finding on magnetic resonance imaging (MRI). Double pituitary adenomas are very rare, and they account for 1% of all pituitary adenomas in autopsy series and up to 2% in large surgical series. In this case report we planned to present a case of double pituitary adenoma that was rare.
Case
A 53-year-old female patient was admitted to another center 6 years ago because of menstrual irregularity. Due to the high prolactin levels and the presence of pituitary adenoma on sella MRI, treatment with cabergoline 1 mg/week was started. The patient applied to our polyclinic after using the drup for one year. Patient complained of frequent menstrual irregularity when she referred to our outpatient clinic. She had no galactorrhea. Anterior pituitary hormone examinations revealed that prolactin was 73.3 ng/ml, LH was 5.4 mIU/ml, FSH was 13 mIU/ml, estradiol was 200 pg/ml and progesterone was <0.1 ng/ml. Other anterior pituitary hormones were normal. The sella MRI revealed a 5 mm sized adenoma. The patient was not considered as prolactinoma. Considering that the patient was in the premenopausal state, monitoring without medication was planned. Prolactin levels were gradually decreased in follow-up. After 1 year FSH: 46.7 mIU/ml, LH: 16 mIU/ml and PRL: 35 ng/ml were detected as compatible with menopause. Control sella MRI revealed a 4 mm sized adenoma that caused a convexity to the suprasternal cistern in the left pituitary gland. At the same time, another adenoma with a diameter of approximately 4 mm was observed in the right pituitary gland, near the cavernous sinüs. Monitoring of the patient without medication is continued.
Conclusions
Multipl pituitary adenomas are defined as simultaneous, morphologically or immunocytologically, distinct tumors. These tumors usually are microadenomas and most of them are clinically silent. Double or multiple pituitary adenomas confirmed by preoperative imaging or intraoperative exploration in particular, are considerably rare. MRI are able to identify multiple adenomas in only a few cases. Detailed preoperative imaging will prevent surgery failure in patients whom operation planned.

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EP106

Rare combination of Acromegaly and Klinefelter syndrome

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Acromegaly is a rare disorder usually caused by a benign tumour of the pituitary gland. Long-term presence of elevated growth hormone (GH) and insulin like growth factor I (IGF-I) levels accompanying this disease is associated with complications such as heart failure, cerebrovascular disease, diabetes mellitus, sleep apnoea and arthropathy. Incidence of acromegaly is 3-5 patients per million ***per year. Klinefelter syndrome*** is the most common sex chromosome disorder occuring in about 1/500 live male births. Common physical features include tall stature, reduced muscle tone, small testes, delayed pubertal development, lack of secondary male sex characteristics and gynecomastia. We present a 31-year-old man suffering from both acromegaly and 47, XXY Klinefelter syndrome (KS). The patient was admitted to our Institute with typical acromegalic features. Laboratory tests revealed high level of GH which was not suppressed after glucose administration, high level of IGF-1, low testosterone concentration with high concentation of gonadotropines. A magnetic resonance imaging scan revealed a $25\times18\times18$ mm macroadenoma involving the pituitary gland. A diagnosis of acromegaly was established. After this examination trans-sphenoidal resection was performed. Histopathologic and immunohistochemical findings revealed growth hormoneproducing pituitary adenoma. The presence of infertility with clinical features such as small testes, lack of secondary male sex characteristics and laboratory findings revealed hypergonadotropic hypogonadism that could not be explained by the diagnosis of acromegaly. A chromosomal karyotyping revealed a 47, XXY, confirming the diagnosis of KS. Testosterone replacement therapy wasn't begun because of patient disagreement. The rare finding of the combination of Acromegaly and Klinefelter syndrome suggests the need for rigorous examination of each patient by a "clear" endocrinopathy.

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EP107

Could it be recurrent immunoglobulin G4-associated inflammatory mass at the hypothalamic region?

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Case
Thirty seven years old patient whose complaint was head ache was seen in the out patient clinic for the follow up of her hormone replacement therapy. First time she was admitted to hospital with the complaint of confusion was in 2013. Her cranial MRI revelaed enlargement of optic chiasma with the possible diagnossis of optic chiasmatic glioma. Biopsy was taken out from this mass twice in July and November of 2013. In histological examinations, there were B and T lymphocytes, eosinophils and histiocytes. Lymphoid malignancies was rulled out by IHC staining. The patient has the diagnosis of panhypopituitarism since 2013. She was taking cortisol, l-thyroxine, desmopressin replacement therapies. Since she had pulmonary thromboembolism in her past medical history, estrogen replacement was given as transdermal estrogen. She has also been using insulin treatment for diabetes mellitus. Recently, her state of consciousness decreased and has been operated urgently, in another health institution. The preoperative pituitary MRI revealed that there was contrast enhancement around hypothalmic-chiasmatic region including pituitary stalk. Cranial MRI showed a lesion located at right caudate nucleus measured as 2.5×1.6 cm in diameters causing edema in white matter. Histopathology was consultated with the pathologist of our center and it was reported as infiltraiton of lymphocytes, plasma cells and histiocytes. It was stated that IgG4 positivity ($>$ 50%) of plasma cells could be taken as a sign of "IgG4 associated disease".
Conclusion
Recurrent mass lesions at the suprasellar region could be due to IgG4 associated disease. Immunosuppressive treatment should be discussed with this possible diagnosis.

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EP108

Rheumatoid arthritis, acromegaly, primary hyperparathyroidism – what's next?

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Introduction
Rheumatoid arthritis is an inflammatory disease characterized by joint destruction, the erosion being caused by invasion of articular cartilage by the synovial pannus. This chronic systemic disease affects approximately 0.5–1% of the adult population, occurring more often in women than in men (3:1). The etiology is thought to be multifactorial, environmental factors or infectious agents being suggested to play a role, but their contribution is yet to be defined. Acromegaly is a chronic endocrinopathy characterized by hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), most likely caused by a pituitary adenoma. Primary hyperparathyroidism is a disorder of one or more of the parathyroid glands, characterized by an elevated PTH that causes hypercalcemia.
Case report
A 57 year old female patient, Caucasian, with no significant family history, non-smoker, diagnosed in 2007 with rheumatoid arthritis (treated with sulfasalazine, methotrexate and leflunomide) and acromegaly (caused by a pituitary macroadenoma of 1.5/1.5/1.4 cm, treated with surgery, gamma-knife, lanreotide and octreotide – medical treatment interrupted 5 years ago), was admitted to our department with recent history of thoracocentesis (rheumatoid pleural effusion

with low glucose level and present rheumatoid factor). The medical history included hypertension, osteoporosis, total histerectomy, sleep apnea and multinodular goiter with hypothyroidism. Clinical examination showed acromegaloid facial appearance, bilateral ulnar deviation of fingers, morning stiffness, swollen and painful joints, swan neck finger deformity, absent breath sounds in the lower 1/3 left hemithorax and a small goiter. Blood tests depicted normal TSH, elevated PTH (80.15 pg/ml), slightly elevated calcium (10.0 mg/dl), insufficient 25-OH-Vitamin D levels (14.75 ng/ml) and a normal IGF-1 (167 ng/ml). Thyroid ultrasonography revealed multiple micronodules with calcification and a hypoechoic mass lesion of 0.7/0.5 cm at the posterior aspect of the right thyroid lobe, resembling a parathyroid adenoma. A small-medium left pleural effusion was noted on chest X-ray without drainage recommandation. Thus, we confirmed the current inactive status of the acromegaly and the absence of pituitary gonadotropin and thyrotropin insufficiency. Treatment was initiated with Zolendronic acid and Vitamin-D 2000 UI/day.

Conclusion

Although genetic testing for multiple endocrine neoplasia syndrome type 1 and type 4 could not be performed, the simultaneously diagnosis of acromegaly and rheumatoid arthritis, associated with the latter presence of primary hyperparathyroidism, arise questions about the occurence of both autoimmune and neuroendocrine pathogeny in the same patient.

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EP109

Ectopic clival prolactinoma with empty sella in a patient using antipsychotic

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Prolactinoma is the most common cause of chronic hyperprolactinemi and drugs that rise serum prolactin levels have been ruled out. Altough almost all of them arise within the sella turcica, there are some rare cases in which prolactinoma is located outside the intrasellar region, so it is defined as ectopic prolactinoma. Neuroleptics (e.g., haloperidol, chlorpromazine, risperidone.) can elevate serum PRL to levels that usually are detected with prolactinomas. We report a case ectopic prolactinoma within the clivus with empty sella in a patient using risperidone and paroxetine.

Case

A 46-year-old woman was referred to the endocrinology clinic for investigation of her clinical presentation of galactorrhea and amenorrhea. She had been taking risperidone two years for the treatment of psychosis. During the admission the physical and neurological examinations of the patient were normal. The complete blood count values and basic serum levels of the biochemical parameters were normal. The hormonal parameters were as follows: St4 12.9 pmol/l (normal referece;12.8–20.4), TSH 1.52 uIU/ml (0.4–3.77), IGF-1 92.9 ng/ml (74-196), and GH 0.014 ng/ml (0—5), FSH 0.7 IU/l (3.5–12.5), LH 0.9 IU/l (2.4–12.6), estradiol 14.6 pg/ml (5–54.7), PRL $>$470 ng/ml (6–29.9). Medication-induced hyperprolactinemia was suspected, and after psychiatric consultation, paroxetine and risperidone were stopped and aripiprazol was begun. After 30 days, her prolactin level was again $>$470 ng/ml and after withdrawing the medications, her symptoms not resolved. Pituitary MRI showed homogeneously enhancing mass within the clivus and basisphenoid associated with an empty sella (figure A,B,C). A mass at the level of the clivus with empty sella, combined with very high prolactin levels, suggested the diagnosis of an ectopic prolactinoma. Because of ammnorhea, possibly due to this tumour, the patient was treated with the longacting dopamine agonist, cabergoline, in a dose of 2×0.5 mg weekly. Prolactin levels dropped from $>$470 ng/ml to 405 ng/ml in four weeks and to 214 ng/ml in eight weeks and to 16 ng/ml in twelve weeks.The treatment was well tolerated by the patient and complaints of galactorrhea and amenorrhea subsided, with the normalisation of the prolactin levels. A control MRI after 6 months illustrated a minimal reduction in the volume of the adenoma (Figure D). The dose of cabergoline was reduced after six months to 0.5 mg weekly, with the continuation of normal prolactin levels.

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EP110

Clinical profile of patients with hyperprolactinemia: a study based on nepalese population

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Background

Hyperprolactinemia is a common endocrine disorder. Yet, data on clinical profile of Nepalese patients with hyperprolactinemia is missing. The aim of this study was to assess the clinical profile of Nepalese patients with hyperprolactinemia.

Methodology

Retrospective clinic based study conducted at the endocrine centre Kathmandu Diabetes and Thyroid Center, Lalitpur, Nepal, in which data was collected from the patient record files of the subjects diagnosed with hyperprolactinemia within the last one and a half year (March 2013 to October 2014). The data was calculated as mean and percentage frequency.

Results

A total of 30 patients diagnosed with hyperprolactinemia(mean prolactin 145.36 ± 145.53 ng/ml) were included in the study. Mean age of the patients was 27.3 ± 7.3 years. Menstrual irregularity was the most common presenting problem (48%), followed by galactorrhea (34%). 14% had infertility and 7% had visual disturbances.10% each had hypothyroidism and PCOS. Pituitary adenoma was demonstrated in 37% patients and idiopathic hyperprolactinemia was seen in 33%. Drug induced hyperprolactinemia accounted for 10% of the total cases. Cabergoline was used in 92% and Bromocriptine was used in 8% patients for treatment of hyperprolactinemia.

Conclusion

Menstrual irregularity and galactorrhea were the most common presenting problems seen in hyperprolactinemia patients. Pituitary adenoma was the most common cause of hyperprolactinemia in Nepalese patients. Cabergoline was the drug of choice for treatment of hyperprolactinemia.

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EP111

GSP gene mutation in a sample of Iraqi acromegalic patients and their response to long-acting repeatable octerotide

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Patients and methods

190 acromegalic patients are registered in the National Diabetes Center, 60 were enrolled in the study. They were randomly selected by simple sampling technique according to their scheduled visits monthly to receive - long acting repeatable octreotide injections (LAR).

Results

Table 1 Demographic data of the enrolled acromegalic patients.

	All subjects	Males	Females
Number	60	32	28
Age (mean ± SD) years	46.35±10.81	46.3±10.9	46.3±10.8
Duration (mean ± SD) years	10.44±6.5	10.5±6.7	10.4±6.5
Minimum duration years	1 month	6 month	1 month
Maximum years	30 years	30 years	20 years

Table 2 Those harboring micro or macroadenoma.

	Patients with mutation	Patients without mutation	*P*-Value
Number	28	32	
Males number (%)	14 (50%)	18 (56.25%)	0.7293
Females number (%)	14 (50%)	14 (43.75%)	0.7449
Macroadenoma	22 (78.5%)	25 (78.12%)	0.9751
Microadenoma	6 (21%)	7 (21.87%)	0.9708
Trans-sphenoidal hypohysectomy	8 (28.5%)	15 (46.87%)	0.4031
No hypophysectomy	20 (71.4%)	17 (53.12%)	0.2576

Table 3 The response rate to octerotide in acromegalic patient and with.

		Patient with no mutation	Patient with mutation	*P*-value
	Number	32	28	
Response	Full responder	18 (56.25%)	14 (50%)	0.7293
	Partial responders	12 (37.5%)	7 (25%)	0.5872
	Non responders	2 (6.25%)	7 (25%)	0.5861

Table 4 The response rate to octreotide.

		Patient with A mutation	Patient with non mutation	*P*-value
	Number	20	8	
Response	Full responder	8 (40%)	6 (75%)	0.2094
	Partial responders	6 (30%)	1 (21.5%)	0.8722
	Non responders	6 (30%)	1 (21.5%)	0.8722

Table 5 Shows the variable data of those with type A and non A.

	Mutation A	Non A mutation	*P*-value
Number	20	8	
Males number (%)	10 (50%)	4 (50%)	1.0000
Females number (%)	10 (50%)	4 (50%)	1.0000
Macroadenoma	16 (80%)	6 (75%)	1.8034
Microadenoma	4 (20%)	2 (25%)	0.8982
Hypohysectomy	7 (35%)	1 (12.5%)	0.6735
No hypophysectomy	13 (65%)	7 (87%)	0.3046

Conclusion

The gold – standard therapy for acromegaly, there is a role for medical treatment by somatostatin analogues as long-acting octreotide (LAR). The response to LAR was found to be affected by *gsp* gene mutation on chromosome 20 in a sample of Iraqi acromegalic patients. *gsp* gene mutation was found to reduce the response to LAR versus those with no mutation, however deletion of cystine in codon 196 of exon 8 was found to be favorable by increasing the percentage of full respondents to LAR versus other types of mutation.

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EP112

Quality of life of patients with active acromegaly which didn't underwent surgery

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Acromegaly is chronic disease caused by hypersecretion of growth hormone (GH), most common caused by adenoma of pituitary gland. Cardiovascular risk, respiratory complication and malignancy are more common in this patients. Most often onset is between 30 to 50 years old, equally between gender. Therapy is almost always surgery, it can be combined with radiotherapy and gamma knife. Medicament therapy with somatostatin analogues, dopamine agonists and GH receptor antagonist. Goal is to show quality of life of patient that didn't underwent surgery treatment, with active acromegaly, aged 84 on analogs of somatostatin therapy for 12 years. Materials and methods: A case report. We used AcroQol questionnaire form on the start of disease and 10 years after.

Conclusion

Acromegaly is rare disease. In active form it is associated with significant morbidity and mortality. In our case during the follow up we diagnosed diabetes mellitus, hypertension, diastolic heart dysfunction stage I and cholecystectomy was preformed because of calculus (probably side effect of octreotide). Based on AcroQol questionnaire in 84 years old patients we conclude that in the beginning of the disease quality of life was reduced because of psychological characteristic/appearance (score −12, 5 vs −3, 4). Over the years condition is changing and physical characteristics were more dominant (score −3, 6 v.s. 0), which can be explained with patients age. Somatostatin analogs therapy in our case is efficient even after 12 years. Glycoregulation is good, and diastolic dysfunction is stable.

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EP113

Serum concentration of insulin-like growth factor I (IGF-I): reference values for adult Romanian population: Preliminary results

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Background

Growth hormone, age, sex, genetics or nutrition status play an important role in insuline-like growth factor 1 (IGF-1) liver production and serum levels. Currently, there is no IGF-I reference range for Romanian population.

Aim

To define sex- and age-adjusted reference values for serum IGF-I measured by an automated chemiluminescence immunoassay in adult Romanian population of healthy subjects.

Methods

The study included 174 adult healthy subjects (148 females and 26 males) from the general population of an urban area in Romania. Exclusion criteria are a body mass index below 18 kg/m2 or over 30 kg/m2, fasting blood glucose over 125 mg/dL, chronic kidney disease stage III or more or liver function test over 2 times the upper limit of normal. IGF-I was measured using a Liaison XL IGF-I chemiluminescence assay (DiaSorin, Sallugia, Italy).

Results

For females median (5, 95 percentile) were 200 (172, 323) ng/mL, 197 (110, 297) ng/mL, 165 (104, 265) ng/mL, 154 (83, 234) ng/mL, 153 (83, 218) ng/mL, 156 (81, 228) ng/mL, 153 (61, 224) ng/mL, 139 (29, 241) ng/mL for 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54 and 55–59 age groups respectively. Due to the small number of subjects median values for age groups in male population could not be calculated. For age-IGF-1 correlation Default (r, p) were $-2.1893x+251.85$ (-0.42, <0.001) and $-0.7321x+184.18$ (-0.17, 0.40) for females and males, respectively.

Conclusion

Reference values for age groups in female adult population of Romania were preliminary defined. Age dependency of IGF-1 was confirmed.

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EP114

Hyponatremia as a first symptom of hypopituitarism due to pituitary metastasis of gastric cancer: Case study

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Introduction

Hypopituitarism can be caused by a number of different etiologic factors including metastatic cancer. Metastasis to the pituitary gland is rare, accounting for only 1.8% of all metastases, and is often detected incidentally by symptoms associated with hormone dysfunction like hyponatremia. Breast and lung cancer are the primary neoplasms with well established properties of pituitary infiltration. Metastases from gastric cancer are unusual and constitute less than 2% of pituitary gland metastases.

Case study

37-year-old woman with 7-month history of gastric cancer (adenocarcinoma tubulare without HER2 amplification), treated with capecitabine, epirubicin, and oxaliplatin based chemotherapy formulation was admitted to the ER due to persistent headache and nausea. Laboratory results revealed hyponatremia (125 mmol/l) and pancytopenia presumably due to chemotherapy. During admission she complained of generalized fatigue and was hypotensive. She had a history of secondary amenorrhea. She was admitted to Endocrinology Department to conduct differential diagnosis of hyponatremia. Laboratory work-up revealed panhypopituitarism with low ACTH, cortisol, TSH and free thyroid hormone levels as well as decreased prolactin, gonadotrophin and IGF-1 concentrations. Diabetes insipidus was absent and the function of the posterior lobe of the pituitary gland was preserved. MR imaging confirmed the pituitary involvement showing a 35×15mm mass infiltrating sella turcica and suprasellar cistern. She

received hydrocortisone and L-thyroxine hormone replacement therapy with significant improvement of her clinical status (stabilization of blood pressure, correction of hyponatremia), and was referred to Oncology Department for further treatment.

Conclusions

Hypopituitarism due to pituitary metastasis is a rare complication of gastric cancer. The possibility of pituitary metastasis should always be considered in patients with malignant tumors, who present with hyponatremia or other symptoms suggestive for endocrine dysfunction. The early diagnosis and introduction of appropriate hormone replacement therapy treatment improves the quality of life and can possibly prolong survival.

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EP115

Macroprolactinemia diagnosed in a patient evaluated for primary infertility

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Introduction

Hyperprolactinemia is associated with suppression of the hypothalamic-pituitary-gonadal axis and it's a frequent cause of infertility, occurring in about 30–40% of infertile women. The bioactive fraction of prolactin is a 23-kDa monomer. However, there are other isoforms with reduced or absent bioactivity, such as macroprolactin, which can be detected by the precipitation reaction by polyethylene glycol. Macroprolactinemia should be suspected in the presence of asymptomatic hyperprolactinemia.

Clinical case

33-year-old woman referred to the Endocrinology appointment in April 2014 for hyperprolactinemia detected during the study of primary infertility with 7 years of evolution. Past medical history irrelevant. The age at menarche was 13, she had regular menstrual cycles, 0G 0P. She had been treated with bromocriptine from June 2011 to June 2013. Since then she took no pills. She had no galactorrhea or hirsutism. Biochemical study during follicular phase: normal renal and liver function, TSH 2.27 mIU/l (0.27–4.20), free T4 20.9 pmol/l (11.7–21.7), FSH 7.7 mUI/ml, LH 5.42 mUI/ml, estradiol 65.6 pg/ml, prolactin 1630 mU/l (127–637), total testosterone 0.17 ng/ml (0.06–0.82), delta 4-androstenedione 2.52 ng/ml (0.30–3.30), cortisol 606.2 nmol/l (171–536), ACTH 18.8, IGF-I 197 (109–324), 17-hydroxyprogesterone 0.7 ng/ml. Progesterone in luteal phase was 16.9 ng/ml (1.7–27.0). Prolactin levels remained high in subsequent measurements (1391, 1158 and 1133 mU/l). Pituitary MRI in 6/2013 and in 10/2014 were normal. Since she had asymptomatic hyperprolactinemia and normal pituitary MRI, we searched for macroprolactin that was positive (percentage of prolactin recovery - polyethylene glycol precipitation: 8%).

Discussion

This case reveals the difficulty of etiological diagnosis of hyperprolactinemia in a woman with a history of primary infertility. However, asymptomatic and slightly elevated levels of prolactin associated with normal pituitary MRI has raised the hypothesis of macroprolactinemia. The diagnosis of this entity was very important to avoid further inappropriate treatment with dopaminergic agonists and to refer the couple to medically assisted reproduction treatment.

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EP116

Clinical characteristics and management of 4 patients with chordomas of the skull base attending Beaumont Hospital

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Introduction

Chordomas are rare slowly growing locally aggressive neoplasms of the bone arising from embryonic remnants of notochord. These tumours typically occur in the axial skeleton and have a proclivity for the spheno-occipital region of the skull base. Parasellar/clivus chordomas account for one third of all chordomas.

Methods

We conducted a retrospective chart review of 4 patients with chordomas of the clivus treated in Beaumont Hospital between 2011 and 2017.

Results

Three of the four patients were male. The median age at presentation was 39 years and the median length of follow-up was 36.5 months. All patients presented with headaches, diplopia and cranial nerve palsies. 6th cranial nerve involvement was noted in all cases at the time of the presentation. Magnetic resonance imaging was employed to localise the tumours. 3 of the patients had evidence of local invasion. None of the patients had clinical evidence of tumour metastasis to distant sites. All patients underwent surgery followed by adjuvant high-dose proton radiotherapy. 3 patients had craniotomies, while one patient had EM guided endoscopic trans-nasal tumour excision. There was no post-operative mortality. However 3 of the 4 patients had evidence of post-operative pituitary dysfunction. Recurrence was noted in one patient. Six further surgical excisions were required prior to radiotherapy (time to first recurrence was 22 months). None of the 4 patients returned to their pre-morbid status, as they all have residual cranial nerve palsies.

Conclusion

Chordomas are aggressive invasive tumours. A multidisciplinary approach in a neurosurgical centre is necessary in the management of these rare tumours. The best results in the treatment of chordomas are reported when using surgery and adjuvant radiotherapy.

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EP117

GH/TSH secreting adenoma: a clinical case report: GH/TSH secreting adenoma: a clinical case report

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Case description

A 26-year-old female visited an endocrinologist for the first time in 2014 with complaint of neck swelling. Lab results revealed increased blood level of TSH, initially the diagnosis of hypothyroidism was set and levothyroxine therapy was initiated with consequent addition of thiamazole due to increasing levels of free T4 and TSH. In 2015 the diagnosis of TSH-secreting adenoma was made on the basis of MRI findings (pituitary microadenoma 3.1 mm in size) and laboratory results (TSH 7.8 IU/l, free T4 26.9 pmol/l, free T3 6.6 pmol/l). The patient first visited Moscow Endocrinology Research Centre in 2017. In further clinical observation we revealed new clinical data: patient reported face and hand enlargement for the last two years. Family history: father had enlarged facial features, died at the age of 34 from obstructive sleep apnoea, grandfather also had enlarged facial features. Laboratory tests revealed the data consistent with mixed TSH/GH-secreting pituitary adenoma: free T4 29.6 pmol/l, free T3 10.4 pmol/l, TSH 6.3 mIU/l, IGF-1 327.1 ng/ml (less than 280.0), beta-crosslaps 0.71, SSBG 200.0 nmol/l (less 110.0). Short-acting octreotide treatment resulted in normalization TSH and IGF-1. Thyroid ultrasound revealed single 5 mm nodule, increased thyroid volume - 20,5 ml. DEXA revealed no BMD loss. Lab investigations revealed no evidence on hyperparathyroidism: PTH and calcium levels were within the reference range. Due to the young age of the patient we chose a transnasal transsphenoid pituitary surgery as the first-line treatment. Postoperative histological investigation: pituitary adenoma. In the postoperative period levels of free T4 and T3 normalized, but the level of TSH remained slightly elevated - 3.7 mIU/l. One month after surgery, laboratory data revealed recurrence of hyperthyroidism, somatostatin analogue treatment was initiated.

Genetic investigation

Due to the evidence of familial case, a NGS was performed using the gene panel (*MEN1, CDKN1B, PRKAR1A, GNAS, AIP, SDHA, SDHB, SDHC, SDHD, PRKCA, CDKN2C, CDKN2A, POU1F1, PTTG2*), which revealed following changes: SDHA: NM_004168: exon8:c.G1002A:p.A334A, rs144252500, MAF 0.002; DICER1:NM_177438:exon2:c.A20G:p.Q7R, rs117358479, MAF 0.0035, more likely to be non-pathogenic.

Conclusion

GH/TSH secreting pituitary adenoma is very rare and could be associated with hereditary cause.

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EP118

Antiphospholipid syndrome and pituitary necrosis

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Introduction
Antiphospholipid syndrome (APS) is an acquired thrombotic disorder. It mainly occurs with systemic disease or as a primary disorder. All organs may be involved by thrombosis. But endocrine disorders seen in antiphospholipid syndrome are rare. In the literature, rare cases of hypopituitarism with APS have been reported.
The observation
It is a 27 years old patient who consults for headache with diplopia. The interview underlines galactorrhea with amenorrhea lasting for 12 years. Physical examination revealed a visual field, a central facial paralysis and monoparesis right upper limb. In biology, it has a hyperprolactinemia to 40 times normal and central hypothyroidism. Anticardiolipin antibodies were positive. Synacthen test was normal. Pituitary MRI showed an expansive process parasellar right 3×2 cm, mainly cystic and hemorrhagic, with mass effect on the right cavernous sinus.
Conclusion
APS should be searched for whenever a history of adenoma with apoplexy is found associated with recurrent thrombosis.

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EP119

A rare emergency case in endocrinology: pituitary apoplexy

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Introduction
Pituitary apoplexy is a relatively rare clinical emergency in endocrinology. It results from hemorrhage or infarction in the pituitary gland. This clinical state is characterized headache, vomiting, visual defects, and signs of meningeal irritability.
Case
22-years-old woman was referred to hospital because of predicted haemorrhagic or cystic pituitary adenom in magnetic resonance imaging (MRI). She was married but not a child. She had menstruel irregularity. Her clinical examination was normal except for slightly headache. Pituitary MRI was repeated. It was showed that T2-weighted images measured 12 mm in diameter reveal a nodular appearance with blood-forming blood products forming fluid levels, which was compressing the optic chiasm. Hormonal laboratory results: TSH: 1.36 mIU/ml (0.3–5.8), LH: 2.77 mIU/ml, FSH: 6.15 mIU/ml, prolactin: 45.6 ng/ml, kortizol: 8.98 mg/dl, ACTH: 16.4 pg/ml, GH: 0.05 ng/ml, IGF-1: 118.1 ng/ml. Serum glucose, creatinin, sodium, potassium, calcium, liver enzymes and hemogram were normal. The headache of the patient was getting worse during the clinical follow-up and added visual defects. Visual field test was consistent bitemporal hemianopsia. She was consultated with insistent headache and visual disturbance by neurosurgery and decided operation. During surgery, there was soft suckable grayish mass with evidence of altered blood. Histopathology revealed apoplexy-like pituitary fragments and 0.1 cm diameter predicted pituitary adenoma. Immunohistochemistry revealed positive reactivity for prolactin and negative reactivity for ACTH, TSH, GH, FSH hormones. She showed instantly headache and vision in both eyes improvement during postoperative period. Cabergolin therapy was started.
Conclusion
We present the case of a woman diagnosed pituitary apoplexy during clinical follow-up. Clinical evaluations and MRI findings was important for pituitary apoplexy diagnosis and management.

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EP120

Macroprolactinoma found in obesity setting: case report

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Obesity is growing fast worldwide. Although environmental factors play a major role, endocrine dysfunction may contribute to the weight gain. We report an invasive macroprolactinoma diagnosed in obesity setting. A 35-year-old male was referred to our endocrine outpatient department due to grade 2 obesity (IMC 38.4 Kg/m2). His weight was increasing since the beginning of his professional activity at the age of 20 due to a sedentary lifestyle. On physical examination he had an hypogonadal facies, with sparse beard, pale skin with fine wrinkles on the corner of the mouth and eyes and bilateral gynecomastia without galactorrhea. Descending testis of 4×3 cm were found, but a micropenis (3 cm) was evident. Patient complained of decreased libido and erectile dysfunction. He denied headache or visual disturbances. When blood analysis were performed, hyperprolactinemia of 1121 ng/ml (Reference range: 4–23 ng/ml) and hypogonadotrophic hypogonadism were found. No other pituitary defects were established and serum calcium was within normal values. Selar magnetic resonance (sMRI) showed a macro adenoma of 26 mm in the highest diameter slightly invading the right cavernous sinus and growing downward to the sphenoidal bone. One month after starting of cabergoline 0.5 mg 3 times a week, serum prolactin markedly decreased to 34.8 ng/ml and the patient lost 5% of body weight. He is awaiting a sMRI re-evaluation. Although the relation between hyperprolactinemia and obesity is established, pathophysiologic mechanism is not clearly understood. This case highlights that even when facing an epidemic disease, careful examination is mandatory and clinical suspicion must be paid.

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EP121

Emotional disorders in patients with tumors of diencephalic localization

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Among tumors of the diencephalic region there are: pituitary adenomas, craniopharyngiomas, gliomas, meningiomas and others. They differ in location, histology, clinic with corresponding hormonal disorders. Emotional disorders in the clinic of tumors of the diencephalic region are revealed in 2–67% by the literature. Emotional disturbances with hormone-active pituitary adenomas there are 30–60%, and with non-functioning pituitary adenomas there are ones less than 6%. Emotional disturbances are revealed in 67% of patients with craniopharyngiomas on the background of a decrease in hormonal secretion. Psychopathology can be caused by the localization of lesions/irritation of the brain, histology and, possibly, changes in the level of neurohormones. Pituitary adenomas has the leading place among tumors of the diencephalon localizations. This is 15% of all brain tumors, the 1st and 2nd places are detectable at the age of 15 to 54 years. Hormone-active pituitary adenomas differ by prolactinoma (PRL-secreting pituitary adenomas −35%), acromegaly (GH-secreting pituitary adenomas – 15%), cushing's syndrome (ACTH-secreting pituitary adenomas −10%), thyrotropinoma (TSH-secreting adenomas-1%) and non-functioning pituitary adenomas (40%).

1. Pituitary adenomas with excessive secretion of growth hormone (GH) - Emotional disorders are in 60% of patients, and nonspecific symptoms, mostly asthenia. It is often stable dysphoria - the predominance of "gloomy-spiteful" mood.
2. Pituitary adenomas gland with excessive secretion of adrenocorticotropic hormone (ACTH):

1) Cushing's disease - changeable mood, depression, apathy, sleep disturbance, with visceral symptoms (tachycardia, fluctuations in blood pressure) are in 50%.
2) Nelson's syndrome - a decrease in emotional reactions and motor activity. Patients are apathetic, monotonous, poor in mimic manifestations.

3. Pituitary adenomas with excessive secretion of prolactin (PRL) - emotional disorders, sleep disturbance are in 30%. Nonspecific symptoms of the asthenia in almost a quarter of patients.
4. Pituitary adenomas with excessive secretion of thyroid-stimulating hormone (TSH) - increased emotionality, excitability, changeable mood, with frequent "panic attacks" are in 40%.
5. Non-functioning pituitary adenomas:

a) With hormone-inactive tumors of the pituitary psychopathology is present in 6% patient. There are violations of sleep, changeable mood, weakness, decreased memory.
b) In craniopharyngiomas emotional and personality disorders was in 67%. This is combined with cognitive, motivational and other impairments.

Conclusion
Violations of emotions in the defeat of the diencephalic region are caused by the localization of the tumor with the involvement of the corresponding brain structures in the pathological process.

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EP122

Clinical improvement of hyperglycemia after use of octreotide lar in a patient with acromegaly who presented with nonketotic hyperosmolar state

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A 37-year-old patient with a history of transcranial pituitary surgery because of acromegaly was referred to our clinic with the glucose level 731 mg/dl. she was not using any medication. There was no ketone in the urine and HbA1c was 18.6%. She has 17×16×15 mm of residual macroadenoma on pituıtary MRI with level of GH 17.5 ng/ml and IGF-1 422 ng/ml. She was using 140 units of insulin glargin U300 and 100 units of insulin regular per a day before octreotide LAR injection. After the first week of injection her need for insulin decreased day by day. She was using aproximately 70 units of insulin in a day before the second injection of octreotide LAR. It remains controversial whether or not octreotide impairs the glucose levels in patients with acromegaly. We herein present the use of Octreotide LAR as an adjunctive option for the treatment of hyperglycemia in patient with acromegaly who needs to use insulin immediately.

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EP123

Frequency of associated diseases in risk groups of a syndrome of Cushing in the Khorezm, Namangan and Kashkadarya regions of the Republic of Uzbekistan

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The aim
To study the characteristic of associated diseases in risk groups of Cushing syndrome (CS) in the Khorezm, Namangan and Kashkadarya regions of the Republic of Uzbekistan
Material and methods of investigation
In total in 2017 in the specified regions it was captured within the project of 21990 persons subject to screening of CS from whom 2185 people for further inspection were selected. From 2185 people of men was – 639 (29.2%), women-. 1546 (70.7%). The age of patients fluctuated from 15 to 45 years.
Results
During the screening research at 21 the subclinical Cushingoid was taped. All patients with subclinical Cushingoid are registered and dynamic observation is prescribed. In risk groups such diseases as a diabetes mellitus (3.9%), goiter (2.2%), arterial hypertension (2.2%), an obesity (2.6%), anemia, a syndrome of polycystic ovaries (2.1%), hypothalamus dysfunction (1.2%), disturbances of a menstrual cycle (1.4%) met.
Conclusions
The most frequent disease in risk groups of patients in the Khorezm, Namangan and Kashkadarya regions was the diabetes mellitus (3.9%).

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EP124

The characteristic of the index of body weight in risk groups of a syndrome of Cushing in the Khorezm, Namangan and Kashkadarya regions of the Republic of Uzbekistan

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The aim
To study the characteristic of the index of body weight in risk groups of a syndrome of Cushing in the Khorezm, Namangan and Kashkadarya regions of the Republic of Uzbekistan
Material and methods of investigation
In total in 2017 in the specified regions it was captured within the project of 21,990 persons subject to screening of SK from whom 2185 people for further inspection were selected. From 2185 people of men was - 639 (29,2%), women-. 1546 (70.7%). The age of patients fluctuated from 15 to 45 years.
Results
Patients complained of raising of the ABP – 347 (16,0%), headaches – 105 (4,8%), excess body weight – 721 (33,0%), etc. Thus, the most part of patients complained of excess body weight. Thus, patients in three regions the dominating complaint have obesity – 721 patients (33%). The research of the index of body weight (IBW) at patients showed the following characteristic of degree of an obesity at them. The first degree of an obesity (BMI from 18.5 to 24.9 kg/m^2) was taped at 570 patients (26.0%), from them the man – 188, women – 382. The second degree of an obesity (BMI from 25 to 29.9 kg/m^2) was taped at 130 patients (5.94%), from them the man – 31, women – 99. The third degree of an obesity was found in 43 patients (1,9%), from them the man – 16, women – 27. And, at last, the fourth degree of an obesity is defined at 31 patients (1.4%), from them the man-10, the woman – 21). Thus, 1 degree of an obesity (26.0%) generally met.
Conclusions
The most frequent complaint among risk groups of patients in the Khorezm, Namangan and Kashkadarya regions was the excess body weight (33%).

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EP125

Dynamics of indicators of the questionnaire of QoL AGHD at assessment of quality of life at patients after 3 months and 6 months after operation of transnasal pituitary adenomectomy by the replacement treatment growth hormone Djintropin

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The aim
To study dynamics of indicators of the questionnaire of QoL AGHD at assessment of quality of life at patients in 3 months and 6 months after operation of transnasal pituitary adenomectomy by the replacement treatment growth hormone Djintropin.
Material and methods
The patients (men-10 and women-3, aged from 18 up to 45 years) who were on stationary and out-patient inspection in the Center of Endocrinology, were selected in group of patients with the diagnosed GH deficiency ($n=13$) and received treatment by growth hormone Djintropin.
Results
Against the background of replacement therapy of GR "DjINTROPIN" reliable increase in values of the IGF-1, GR levels in blood ($P<0.05$) in 3 months of treatment and respectively increase in values of the IGF-1, GR levels in blood (P <0.05) and also blood GR ($P < 0.05$) in 6 months has been recorded. Significant reliable increase in level of calcium ($P < 0.05$), phosphorus ($P < 0.001$) and also increase in activity of alkaline phosphatase is noted ($P < 0.01$) indicating acceleration of processes of bone metabolism against the background of the carried-out therapy. Decrease in levels of the general cholesterol and Lipids is recorded that demonstrates beneficial effect of GR "DJINTROPIN" on lipid exchange.
Conclusions
Assessment of change of anthropometrical indicators against the background of the carried-out therapy of GH "DJINTROPIN" has shown normalization of indicators of QoL according to the questionnaire of QoL AGHD: 10.2 ± 2.5 points (during 6 months). Against the background of replacement therapy of GR "DJINTROPIN" reliable increase in initially low values of the IGF-1, GH levels in blood ($P < 0.05$) in 3 months of treatment and also increase in STH ($P < 0.05$) in 6 months has been recorded.

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EP126

Years of Misery: a final resolution 'panhypopituiatirsm'

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We report a case of a 76 year old gentleman referred to the endocrine department by his general practitioner (GP) with a few years history of severe lethargy, low mood, and dizziness on changing posture. He is known to have hypothyroidism, hypertension, hypercholesterolaemia, benign prostatic hypertrophy, and benign colonic polyps. His medications included amlodipine, finasteride, lansoprazole, atorvastatin and levothyroxine. Examination of all systems were unremarkable, in particular neurological examination with no postural drop. A full pituitary profile was performed which showed low free T4, cortisol, testosterone, and IGF-1, indicative of panhypopituitarism. A short synacthen test showed a serum cortisol at 0 and 60 minutes of 57 and 480 nmol/l respectively. He subsequently underwent an insulin tolerance test showing a drop in glucose from 4.8 to 2.0 mmol/l after 50 min, at which point the patient developed symptoms of dizziness and blurred vision. His blood glucose of 2.0 mmol/l was corrected to 4.2 mmol/l with two doses of glucojuice and 100 ml of 20% glucose infusion. A second drop in glucose was observed to 2.9 mmol/l which was corrected to 4.9 mmol/l with two further doses of glucojuice. The insulin tolerance test confirmed cortisol and growth hormone deficiency with flat cortisol and undetectable growth hormone levels. A computed tomography (CT) head scan was arranged instead of a magnetic resonance imaging (MRI) scan as the patient was claustrophobic, and did not reveal any pituitary abnormality. Following commencement of hydrocortisone he has felt much better and awaiting assessment for growth hormone and testosterone therapy.

Conclusion

It is paramount to consider endocrine dysfunction in patients with multitude/non-specific symptoms despite unremarkable clinical examination and normal basic pathological investigations.

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EP127

Prolactinoma and granulomatous mastitis

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Granulomatous mastitis (GM) is an inflammatory lesion of the breast relatively rare with multiple etiologies suggested. Although most cases of GM show an association with breastfeeding and pregnancy, a minority of cases were related to hyperprolactinemia caused either by drugs dopamine antagonists or intracranial lesions, including pituitary adenoma. We report a case of a patient who had GM associated with microprolactinoma. Surgical treatment of the adenoma was indicated because of gastrointestinal intolerance of drug treatment with the effects of hyperprolactinemia on the mammary gland. Indeed it is reported in the literature a complete resolution within the inflammatory lesions and normalization of prolactin response to medical or surgical treatment of brain injury causing hyperprolactinemia, suggesting that it would be the direct cause of GM. Therefore, the authors suggest to detect pituitary tumors and to evaluate the levels of prolactin in the assessment of patients with MG recent history without breastfeeding or pregnancy and in the absence of another identified etiology.

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EP128

Epidermoid cyst of the sella turcica: about a case

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Introduction

Epidermoid cyst (EC) or cholesteatoma is a benign tumor, often of congenital origin. It accounts for 1% of intracranial tumors and is mainly located at the ponto-cerebellar angle and suprasellar, EC takes the aspect of a beaded tumor with nodular surface and white pearly color simulating candle wax. The treatment is surgical taking into account the substitution of endocrine pituitary deficits in this form of description.

Patient and observation

We report the case of the married patient EY, aged 38 and father of two but with no particular pathological history, particularly no cranial trauma. He showed left visual acuity decrease, left temporal headache and vomiting, with anterior pituitary deficiency symptoms of the corticotropic axis such as pallor, asthenia, fluid diarrhea, thyrotoxic such as depilation of the forearm, legs, armpits and pubic, slowing down; and gonadotropic such as libido decrease, 1 year ejaculations and morning erections. Cerebral MRI has revealed craniopharyngioma in the patient. Hormonal checkup revealed corticotropic deficit. Indeed, MRI revealed heterogeneous signal intra and supra-sellar process containing hypo and isointense tissue areas in T1, intermediate in T2, and hyperintense in Flair, with no calcifications; hyperintense multilocular zones in T1, measuring 18 * 15 * 27 mm of major axes, bridging the suprasellar cistern, elevating the optic chiasm and the anterior cerebral A1 segments and extending to the left hypothalamic region. The patient was operated using high temporal approach. Anatomopathological checkup showed a morphological aspect compatible with an epidermoid cyst. Post-operative follow up revealed the appearance of diabetes insipidus for which the patient was put under minirin; gonadotropic, thyreotropic and corticotropic deficiencies were substituted by hormonal treatment, Postoperative eye fundus was in favor of bilateral papillary palate which the patient used to have before, bilateral visual acuity improved to 10/10. Visual cham has remained altered, particularly to the right.

Conclusion

Epidermoid cyst is a benign tumor of slow but inevitable linear evolution and requires surgical treatment. The diagnosis becomes easier, especially with MRI scattering sequences' advent. Such observation argues in favor of the congenital origin and the slow evolution of this type of tumors.

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EP129

Adult onset hypopituitarism – a surprising diagnosis in a postmenopausal women

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Adult-onset hypopituitarism is a frequently delayed diagnosis because of the insidious debut and non-specific symptoms, frequently attributed to normal aging or many other pathologies - fatigue, malaise, cognitive impairment, decreased libido. Left untreated, it can have severe consequences with vital impact.

Case-report

We present the case of a female patient, aged 69, who was initially addressed for evaluation of hypercalcemia. She had had four live births, last one at 38 years and she entered menopause at 54 years old. At the initial evaluation, the patient presented with hypercalcemia and elevated parathyroid hormone, as well as low fT4 and low TSH levels, suggesting secondary hypothyroidism along with primary hyperparathyroidism. Subsequent evaluations revealed also hypogonadotropic hypogonadism. The patient did not associate polyuric-polydipsic syndrome nor secondary adrenal insufficiency. The visual field evaluation was inconclusive due to cognitive impairment and difficult collaboration. There were no pathological changes in the pituitary area on contrast CT scan. She was started on levothyroxine therapy, with mild improvement in cognition. She will undergo DXA evaluation, parathyroid scintigraphy and surgery for hyperparathyroidism. She will remain under surveillance for developing adrenal insufficiency.

Conclusions

What seemed to be a simple case of primary hyperparathyroidism, turned out to be a surprisingly association between two endocrine diseases and a challenging diagnosis because fatigue, malaise and cognitive impairment are non-specific symptoms and could have been all attributed to hyperparathyroidism. Therefore, clinical and laboratory evaluation for hypopituitarism would be recommended in patient presenting with those subtle complaints.

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EP130

Abstract withdrawn.

EP131

Gonadotropinoma without clinical function

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Introduction
Pituitary adenomas are the most common cause of sellar masses. Several types of tumors may involve the sellar region, because of complex anatomy. They are classified according to size, function, immunohistochemical examination cell type of adenomas. Most of the pituitary adenomas without clinical function are gonadotropin-releasing adenomas on immunohistochemical examinations. They are usually seen as macroadenomas. They are often diagnosed with pituitary insufficiency due to adenomatous compression.
Case
A 68-year-old female patient presented with complaints of diplopia and narrowing of the visual field. There was no feature on her resume. No pathology was found on physical examination. A lesion consistent with a 39×30×25 mm adenoma was found on hypophysis MR. The adenomatous cavernous sinus lengthened and there was marked pressure on the optic chiasm. Bitemporal hemianopsy is present in the visual field examination. In laboratory tests panhypopituitarism was detected (Prolactine level is normal). Hormone replacement therapy started. The patient was operated under steroid replacement treatment. Visual function improved after the surgery. The histopathologic report showed an adenoma and immunohistochemical findings were consistent with gonodotropinoma.
Conclusion
In macroadenomas without clinical function, it is recommended to apply surgical treatment to visual field deficit or loss, ophthalmoplegia, optic chiasmal pressure, pituitary hormone deficiency and apoplexy. The aim of surgical treatment is to correct neurological deficits, hormone insufficiency and prevent recurrence.

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EP132

Pitfalls in the management of inadequate TSH in the outpatient endocrine clinic: a case report

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A 34-years old woman was referred to the outpatient clinic due to elevated TSH level during last three years. She was aware on the decreased thyroid function due to autoimmune thyroiditis since she was 24-years old. At that time L-thyroxine was introduced to the patient in a daily dose od 75 μg. Since elevated TSH up to 6.3 mU/l was noticed, she experienced frequent temporal headaches, noticed enlargement of hands, lips and nose, and increased shoes size. However, menstrual cycles remained regular. At the first visit, her hormone profile showed FT4 13.0 pmol/l and TSH 5.1 mU/l on the daily L-thyroxine of 150 μg. As the pituitary tumor was suspected, patient was send for contrast MR of the pituitary gland that showed an existence of macroadenoma of 17×12×11 mm in diameter. Additional analyses revealed IGF1 of 992 ng/ml, growth hormone of HR 5.0 mU/l with normal prolactin, cortisol and ACTH. No additional functional tests were performed. Echocardiography was normal while abdominal ultrasound showed slightly enlarged spleen (13×5.6 cm). The neurosurgeon has been consulted and the patient was sent for the surgical procedure. Transsfenoidal adenectomy was performed in the Departent for neurosurgery without post-operative complications. Pathohistological examination with immune-histochemical staining confirmed gowth hormone secreting pituitary adenoma. Post-surgical hormone profile showed TSH 0.88 mU/l, FT4 12.9 pmol/l, cortisol 443.8 nmol/l, IGF1 119.9 ng/ml and GH 0.14 mU/l. Patient continued with daily therapy with 100 μg of L-thyroxine, and was lost from further follow-up. In conclusion, prolonged inadequate TSH during high L-thyroxine therapy should be suspicious for TSH-secreting pituitary adenoma. This case was lacking in proper functional diagnosis before operation, adequate immune-histochemical staining on TSH and Ki-67 for the assessment of possible mixed forms and it's aggressiveness, and proper post-surgical follow including functional testing and MR of the pituitary.

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EP133

Galactorrhoea, severe anxiety and an unexpected outcome

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We report a case of a 43 year old lady who was referred by her general practitioner (GP) to the endocrine team with an 8 month history of extreme fatigue, difficulty losing weight, galactorrhoea and mild breast enlargement. She has two children aged 16 and 14, all well. Her background medical history included depression, asthma and hysterectomy for fibroids 3 years ago. Examination of all systems were unremarkable including visual fields to confrontation, fundoscopy and full neurological exam, except for a drop of milky discharge on expressing nipples and a palpable right thyroid nodule. She was investigated by means of a pituitary profile which showed prolactin of 768 mainly monomeric (upper limit 496), E2 <44 with the remainder of her pituitary screen being normal. A subsequent magnetic resonance imaging (MRI) scan showed a bulky pituitary gland but no definite lesion/adenoma. Her galactorrhoea subsided on cabergoline which was stopped at 6 weeks. She then reported bilateral galactorrhoea after cessation of cabergoline. It was a joint decision to take a wait and see approach, with repeated blood tests earlier if need be. Her thyroid ultrasound showed a 5 mm U3 nodule with FNAC reported as THY4. In view of the high suspicion of malignancy she was referred to the endocrine surgeon following endocrine MDT meeting. As part of her pre-operative work up, a chest x-ray showed an incidental finding of a possible mass in the right atrium. She was further investigated with a computed tomography (CT) scan of the neck, chest, abdomen and pelvis to assess the atrial mass and for routine staging. This showed a 5 mm hypo enhancing nodule in the thyroid isthmus with no evidence of malignancy, an incidental finding of a 7 mm left adrenal nodule and a 2.5 cm×2 cm soft tissue mass attached to the atrial septum suggestive of an atrial myxoma. An echocardiogram showed a strong possibility of atrial myxoma, hence she was referred to the cardiothoracic surgeons for further assessment and surgical excision after confirmation of normal urinary metanephrines. She is awaiting total thyroidectomy in view of cytology findings (THY4).
Conclusion
The importance of a good thorough history and examination of all systems is paramount as it can reveal other incidental findings which may well then have an impact on future comorbidities, mortality and ones life.

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EP134

A case of acromegaly and Cushing's syndrome

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We herein describe a 55-year-old woman who showed a dramatic improvement in glucose control following treatment for co-existing acromegaly and Cushing's syndrome. The co-occurrence of acromegaly and Cushing's syndrome in one individual is extremely rare. This patient was diagnosed as having diabetes mellitus 7 years ago. Afterwards, in spite of insulin therapy, her hyperglycemia could not be well controlled. Endocrinological and radiological examinations revealed subclinical adrenal Cushing's syndrome. Successful treatment for these endocrinopathies resulted in greatly improved blood sugar control because of a reduction in insulin resistance. The insulin treatment was discontinued following the treatment of acromegaly. This report describes insulin resistance before and after treatment in a case of acromegaly accompanied by adrenal preclinical Cushing's syndrome.

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EP135

Clinical and diagnostic features of prolactinomas

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Relevance
Prolactinoma is an adenoma of the pituitary gland with the production and secretion of prolactin (PRL) in varying degrees, almost always benign, but, nevertheless, often clinically significant and causing difficulties in treatment. Often prolactinomas are classified according to size as microadenomas (less than 10 mm in diameter) or macroadenomas (more than 10 mm in diameter). More than 90% of prolactinomas are small, intrasellar tumors that rarely increase in size. Sometimes, these adenomas can be aggressive or locally invasive and cause compression of vital structures. Malignant prolactinomas that are resistant to treatment and are dissiminated into I and out of the CNS are very rare. Approximately 40% of all pituitary adenomas are prolactinomas. The age of patients varies widely and there are publications about prolactinomas in patients between the ages of 2 and 80 years. Prolactinomas are common in women with a peak frequency in fertile age. Although often these tumors attract attention after discontinuation of oral contraceptives, there is no correlation between the use of oral contraceptives and the development of prolactinomas. Most prolactinomas in women are presented by microadenomas. About 90% of premenopausal women have oligo/amenorrhea, up to 80% also observe galactorrhea. Inovulatory infertility may also occur in some cases. Pathogenesis of prolactinomas is unknown, but the process may involve an early genomic mutation leading to a mutation in pituitary stem cells. Various contributing factors can stimulate the proliferation of mutated cells. Family forms of prolactinomas were also described, which indicate the possibility of a genetic component playing role in pathogenesis. Prolactinomas are the most common cause of persistent increase of serum prolactin levels, which is more common in women of reproductive age and may be the cause of infertility. The clinical manifestations of hyperprolactinemia vary widely, the symptoms mainly include reproductive, sexual, metabolic and emotional-personal impairments, and in macropolactinoma, signs and symptoms of a volumetric process in the hypothalamic-pituitary region. The method of choice in the treatment of most patients with prolactin secreting pituitary adenomas is drug therapy. Treatment of hyperprolactinemia in prolactinomas is aimed at achieving the restoration of normal prolactin concentration, restoring ovulatory menstrual cycles, restoring fertility in women and men and in improving impaired sexual function in men, and reduction in tumor size.

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Reproductive Endocrinology

EP136

The clinical management and follow-up of adults with Turner's syndrome in University College Hospital Galway

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Background and Aim
Turner's syndrome (TS) or 45 XO is a condition in which a female is partly or completely missing an X chromosome. TS affects 0.025–0.05% of females and can involve multiple organs through all stages of life, necessitating a multidisciplinary approach to care. We aim to evaluate our practice compared to the clinical practice guidelines, which recommends the following: annual BMI, blood pressure, HbA1c, lipid profile, liver function, thyroid function, skin and teeth inspection; 3 yearly serum calcium, vitamin D, echocardiogram; 5 yearly audiometric evaluation and DEXA scan. As appropriate, renal ultrasound, ophthalmologic evaluation, ECG, liver ultrasound, fertility counselling, uterine ultrasound and coeliac screen.
Methods
Online Patient Correspondence System was used to identify patients with TS in University College Hospital Galway (UCHG). Charts were ordered, reviewed and data was collected and analysed on an encrypted excel sheet.
Results
16 patients with TS were identified. Two paediatric patients were excluded. Of the 14 included, three patients were not under endocrine service follow-up and 1 patient had follow up in another hospital. The following are the compliance to management guidelines; 86% echocardiogram, 36% cardiac MRI, 95% blood pressure measurement, 71% lipid profile, 36% DEXA scan, 86% serum calcium, 50% serum vitamin D, 93% liver function test, 79% HbA1c, 100% thyroid function test, 64% coeliac screen, 71% renal ultrasound, 29% audiology testing, 36% fertility discussion, 64% HRT, 14% uterine ultrasound, 14% dermatology review, 0% orthodontic, ophthalmology and psychiatric evaluation.
Conclusion
We are planning to use a standardised proforma and re-audit the patients, to improve the management of Turner Syndrome in University College Hospital Galway.

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EP137

Etiological profile of premature ovarian failure: about 42 cases

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Introduction
Premature ovarian failure (POF) is defined as amenorrhea lasting more than four months before the age of 40 with a high level of gonadotropins in at least two separate samples. The aim of this work was to describe the etiological profile of a series of Tunisian women followed for POF.
Patients and methods
It is a descriptive study of 42 cases of POF collected in the endocrinology department of Sousse between 2000 and 2017.
Results
The average age of the patients was 23.85 years old. Thirty patients consulted for primary amenorrhea with an average age of 18.8 years and 12 patients consulted for secondary amenorrhea with an average age of 36.5 years. Eleven patients reported irregular periods before the installation of secondary amenorrhea while the beginning was brutal in the twelfth. A family history of primary sterility was found in two patients, a family autoimmunity field was found in two patients, whereas no history of early menopause was found in our patients. Nine patients were followed for type 1 diabetes, six patients for primary hypothyroidism and one patient for celiac disease. The hormonal profile showed an average FSH level of 90.7 mIU/ml, an average LH level of 49.82 mIU/ml and an average estradiol level of 21.42 pg/ml. The karyotype was requested in all patients who consulted for primary amenorrhea. It showed a mosaic Turner syndrome in two of our patients. In addition, the immunological survey showed positive anti-ovarian antibodies in one patient. At the end of this investigation, an autoimmun origin of POF was retained in 38% of patients and a genetic origin related to Turner syndrome in 4,76% of patients. The POF was idiopathic in 57,24% of our patients.
Discussion and conclusion
The POF is not an exceptional pathology. The most commun etiologies are at the present time sterilizing treatments such as chemotherapy or radiotherapy. Genetically, abnormalities of the X chromosome, in particular Turner syndrome, are identified. Most often, after a thorough clinical investigation, no etiology is found. Indeed, idiopathic POF still accounts for more than 75% of cases.

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EP138

Evaluation of dynamic thiol-disulphide homeostasis in healthy postmenopausal women

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Introduction
The purpose of this study was to evaluate the relation between menopausal women and the thiol/disulphide balance, used as a marker of oxidative stress, by measuring that exchange using a novel technique.
Methods
Fourty five postmenopausal subject and 39 healthy participant were included in the study.
Results
We found that in postmenopausal group, disulphide ($P=0.04$), disulphide/native thiol ($P=0.004$), disulphide/total thiol ($P=0.004$) were higher than the control group, in postmenopausal group, albumin ($P=0.008$), native thiol ($P=0.007$), total thiol ($P=0.016$) and native thiol/total thiol ($P=0.004$) were lower than the control group with independent of age. Furthermore, a positive correlation was determined between albumin and native thiol ($r=0.425$, $P=0.000$), total thiol levels ($r=0.416$, $P=0.001$). We found negative correlations between native and total thiols and inflammatory parameters white blood cell (WBC) ($r=-0.371$,

$P=0.001$ – $r=-0.390$, $P=0.001$), neutrophil lymphocyte ratio (NLR) ($r=-0.306$, $P=0.008$ – $r=-0.293$, $P=0.011$).
Conclusion
This study showed that postmenopausal phase is associated with oxidative stress. Our study supports the hypothesis that decreased albumin and inflammation might be the major cause of oxidative imbalance.

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EP139

Correlation of LH and FSH with serum TSH levels in polycystic ovarian syndrome

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Background and objectives
PCOS is the most common endocrine disorders among women between the ages of 17 and 44. It affects approximately 5% to 10% of this age group. It is one of the leading causes of poor fertility. PCOS patients usually develop thyroid disorders which have an adverse effect on fertility and other hormones. Hence this study was done to estimate levels of LH, FSH, and TSH hormones and to find a correlation between LH,FSH and TSH levels.
Study population
A total of 50 patients of age group 17–44 years were studied for the six months. The patients were included if they satisfied the diagnostic criteria suggested by Androgen Excess PCOS Society. They were excluded if they were having DM II. Hypertension, liver disorders,renal disorders and other chronic diseases. After informed consent and brief clinical history, examination was done to rule out renal disorders, liver disorders or any other condition that would affect the parameters under study. LH.FSH and TSH was estimated. We study a group of patients who are diagnostic with PCOS. In this group we estimate LH, FSH, TSH. Normal levels of FSH is 3–20 mIU/ml, LH <7 mIU/ml, TSH .4–4 uIU/ml.
Interpretation and conclusion
The results of our study showed that levels of LH were high in patients with PCOS with ratio of LH/FST $>2:1$. Though there is a positive correlation between LH and TSH in both age group it is more significant in older group.TSH levels were high in cases which signifies the evaluation of thyroid function in PCOS patients Thus It was concluded that in PCOS diagnosed patients we should evaluate thyroid functions along with hormonal evaluation to prevent further infertility.

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EP140

Ameliorating effect of Cuscuta japonica chois (CJC) extract on hind-limb ischemic mice

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Cuscuta japonica chois (CJC) has been used traditionally to treat sexual disorder and skin problem such as pimples, freckles and melasma in Korea. The present study aimed to investigate the alleviating effect of CJC extract on surgical injury-induced ischemia in the hind-limb of mice. In this study, Female C57BL/6 mice were ovariectomized and excised the vessels of hind-limb after ligated by surgical silk (6-0). The mice were administered with CJC (150 or 450 mg/kg per day) for 3 weeks and blood blow rate was evaluated using a laser Doppler system at -7, 0, 7, 14, 21 days after hind-limb ischemia. The serum profiles of angiogenetic factors and inflammatory factors were measured by antibody array, and its transcript-level were evaluated by RT-PCR. The blood flow rate was normalized with non-ischemic lesion, and the rate was significantly elevated at 14 and 21 days after hind-limb ischemia compared with the vehicle group. The density of capillaries was also significantly increased by CJC treatment in a dose-dependent manner. In addition, CJC up-regulated the transcriptional expression of angiogenetic factors including ET-1, ANGPT-1 and IGFBP-3, whereas, the inflammatory cytokines, TNF-α, IL-6 and IL-1b were down-regulated in the hind-limb of mice. These results of present study assumed that CJC extract may have therapeutic potential in the treatment of hind-limb ischemia due to its peripheral angiogenesis and anti-inflammation in mice.

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EP141

Differences in the use of contraception between Roma and non-Roma women in Hungary

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Objective
The purpose of this study was to investigate the contraceptive practice and sociodemographic determinants of employment of contraceptive methods among sexually active Roma and non-Roma women.
Design and methods
This research included 133 Roma and 687 non-Roma women aged 18–26 from secondary schools Szeged. Women completed self-report questionnaires on sociodemographic characteristics, contraceptive practice and sexual activity between 2015 and 2017. Oral contraceptives, intrauterine devices, male/female sterilization, vaginal ring, plaster, implant and injection were regarded as reliable methods, while barrier methods, periodic abstinence, withdrawal, spermicides, vaginal douche or no method were considered less reliable methods based upon the Pearl index. Multivariate logistic regression analyses were used to analyze socio-demographic factors associated with the use of contraception and unwanted pregnancy in both population groups.
Results
The mean age of the women was 25.4 years (± 8), and 77% reported urban residents. The rate of use of reliable methods (hormonal contraceptives, intrauterine devices or sterilization) was 43%, while no method was used by 4.7% of the participants. Most women were married or lived in a long-term relationship (74.9%). Roma women are less educated than non-Roma women ($P<0.001$) Roma women use any type of contraception more often than non-Roma women. However, Roma women rely more on traditional and unsafe methods such as withdrawal and lactational amenorrhea method, but significantly less on modern methods such as pill, condom and intrauterine device ($P<0.001$).
Conclusion
Promoting reliable contraception methods and to organise educational courses about the importance of the use reliable contraceptive methods should be in the focus of national health policies and strategies related to reproductive health to reduce these ethnic differences and inequalities.
Funding statement
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EP142

Atypical presentation in a patient with 45,X/46,X,i (X) (q10) Isochromosome Xq in mosaic turner syndrome: a case report

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Isochromosome Mosaic Turner Syndrome (IMTS) is a variant of Turner Syndrome (TS) characterized by cytogenetic profile of 1 or more additional cell lineages aside from 45,X, and the presence of a structurally abnormal X chromosome consisting of either two short or two long arms. IMTS is rare, with only 8–9% prevalence among women with TS based on international studies, and 15% of all TS in the Philippines. A 20 year old female came in due to amenorrhea and alopecia. Physical examination revealed short stature, cubitus valgus and Tanner Stage 1 pubic hair and breast development. Transrectal ultrasound revealed absent ovaries and infantile uterus. Hormonal evaluation revealed hypergonadotropic hypogonadism. Bone aging was that of a 13 year old for females with non fusion of epiphyseal plates. Cytogenetic study revealed 45,X [37]/46, X, i (X) (q10) [13]. This is consistent with a variant Isochromosome Mosaic Turner Syndrome. She was screened for medical complications. Audiogram and two-dimensional echocardiography were unremarkable. She has dyslipidemia and was given statins. She has subclinical hypothyroidism with positive test for anti-thyroglobulin antibody. Her intelligence quotient (IQ) was below average. She received incremental doses of conjugated estrogen and progesterone that patterned the hormonal changes in normal menstrual cycle. On the third week of hormonal therapy, she developed breast mound. On the fourth week, she had her first menstrual period. Her alopecia resolved spontaneously. The above case is a rare variant of Turner Syndrome, more so, a presentation of alopecia in IMTS makes it more atypical. This required optimal supportive, medical and psychological care.

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EP143

Serum 25-Hydroxy vitamin D levels and insulin resistance in polycystic ovary syndrome

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Background
The polycystic ovary syndrome (PCOS) is often seen in reproductive age women. Although the ratio of insulin resistance is not knowm definitely in PCOS patients it is thought to be between 50 to 65%. Several studies have shown that low serum 25-Hydroxy Vitamin D (25(OH) D) levels are associated with high body mass index (BMI), insulin resistance, and waist/hip circumference, but it has not yet been clearly determined. In this study, we aimed to determine the correlation between serum 25(OH) D status and metabolic or clinical profiles of the PCOS and non-PCOS groups.
Methods
A total of 40 premenopausal female patients with (mean(SD) age: 26.77 (7.54 years) who were diagnosed with PCOS based on clinical and biochemical evaluation in accordance with revised Rotterdam criteria upon their admission to our clinic with the complaints of excessive hair growth and menstrual irregularity and age matched healthy volunteers (mean(SD) age: 28.10 (4.48) years) were included in this study. Polycystic ovarian morphology was confirmed via in USG in patients. Hirsutism was evaluated using Ferriman–Gallwey score and menstrual disturbance (none, oligomenorrhea, amenorrhea) was evaluated based on medical history in all subjects. Following the physical examination and anthropometric measurements of the patients and healthy subjects, their hormone profiles, glycemic parameters, insulin resistance and 25(OH) D were evaluated. Insulin resistance was evaluated by homeostasis model assessment (HOMA-IR).
Results
PCOS patients are found to be obeser than our control group ($P<0.01$). Plasma glucose levels were significantly higher in women with PCOS than in control group. It is found that homeostatic model assesment (HOMA-IR) which is an indication of insulin resistance is statistically significantly higher in PCOS patients ($P<0.01$). In the hormonal evaluation of the subjects the level of dehydroepiandrosterone-sulphat (DHEA-S) and androstenedione were statistically significant higher in PCOS patients. Vitamin D levels were found to be lower in PCOS patients. When PCOS patients were evaluated as obese and non-obese, vitamin D levels were found to be lower in the obese group ($P<0.01$).
Conclusion
In this study we demonstrate lower levels of vitamin D in PCOS patients. In our study, the detection of lower vitamin D levels in PCOS patients suggested that this may be one of the causes of insulin resistance and metabolic complications in these patients.

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EP144

Endocrine disruption and oxidative stress implications of imipenem therapy in the ovary of 'wistar' rats

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Imipenem (IMP) is a carbapenem antibiotic mainly used to treat nosocomial infection diseases. We aimed to evaluate the oxidative stress of therapeutic doses of imipenem (IMP) on the ovary of 'wistar' rats. In this respect, female rats were divided into four groups: animals were intraperitoneally treated with physiological serum, 30, 50 and 80 mg/kg of IMP for one week. We found that therapeutic doses of this drug did not significantly affect the levels of ovarian malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT). On the other hand, levels of reduced glutathione (GSH) and glutathione peroxidase (GPx) activities in the IMP-treated groups were decreased following the increasing doses of IMP. In addition, oestradiol and progesterone levels were also significantly reduced by IMP therapy compared with the control group ($P<0.05$). The light microscopy evaluation revealed normal ovary parenchyma. These results suggested that IMP induced oxidative stress and disrupt hormonal balance in the rats'ovaries.

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EP145

The combination of cardiovascular risk factors in PCOS and the risk for cardiovascular disease events

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Objectives
- PCOS is defined by the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and the exclusion of related disorders.
- Women are exposed to increased risk for cardiovascular disease, hypertension, type 2 diabetes mellitus and other metabolic complications
- Cardiovascular disease (CVD) is one of the most common cause of mortality worldwide
- Women with PCOS appear to have increased number of risks compared to healthy, age-matched women at any age. The question remains unanswered whether this increased cardiovascular risk in women with PCOS can be translated also to increased cardiovascular events.
- PCOS is not only one of the commonest causes of subfertility in women, but it has also many metabolic consequences. It is associated with insulin resistance and diabetes mellitus, obesity, dyslipidemia as well as alterations of the fibrinolytic system.
- All the above are independent, traditional cardiovascular risk factors that can predispose women with PCOS to early onset CVD.

Methods
- In the next Figure we present the combination and the interaction of the main cardiovascular risk factors in women with PCOS
- The CVD factors included and combined are insulin resistance, androgen levels, systolic blood pressure, body mass index (BMI) and androgen levels.
- This Figure illustrates that women who have many risk factors are, possibly, at increased risk for cardiovascular events
- The different CVD risks are depicted in different colors and the number of co-existing risks that are present in one woman is reflected with the intensity of the color

Discussion
- In this figure is a scheme which combines wellknown CVD risk factors with and without the presence of hyperandrogenemia, a specific dishormonal alteration for PCOS women, reflecting a unifying approach of CVD risk factors in women with PCOS
- This may provide a more individualized assessment of how real is the cardiovascular risk in these women
- It may be used as a tool of assessing the potentiality of multiple interconnections of CVD risk factors linked with cardiovascular events in women with PCOS

Conclusion
- This type of combined presentation of CVD risk factors may prove to be of clinical significance in PCOS, as it could help of real life CVD risk stratification and subsequently prevention or targeted therapeutic management of these patients

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EP146

Endometrioid adenocarcinoma of abdominal wall in histerectomized patient 18 years before

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A 69-year-old patient with a history of hysterectomy 18 years ago due to apparent uterine myomatosis, who presents with a clinical picture of 6 months of evolution

of a solid suprapubic mass without any other associated symptomatology. Normal vaginal cytology 3 years ago; Menarche at 16 years of age and obstetric history: G1P2V2(Twin).
Physical examination
Indurated mass in the suprapubic region, mobile, not painful External atrophic genitalia; Vaginal examination: mass in suprapubic region, solid, mobile, without clarity regarding intrapelvic location; vaulted vagina and uncovered dome. Abdominal-pelvic CT-SCAN: Solid mass that makes body with the abdominal wall located on the midline of suprapubic region reaching diameters of length 6.5 cmx6 cmx10 cm, richly vascularized, with adequate cleavage planes with the surrounding structures and located above of the vesical dome. Tranvaginal-Echography: Absence of uterus due to surgical history, free vaginal dome without masses or collections, right adnexal mass of 55×52×61 mm for a volume of 93 cc, left ovaryof 17×10×15 mm, volume of 1.5 cc, free sac fundus. Tumor markers: Alphaphetoprotein (AFP): 3.6 ng/ml (normal value(NV) < 10 ng/ml (−); CARCINEMBERIONAIRE ANTIGEN(CEA): 4.0 mcg/L(NV < 5 mcg/L) (−); CA-125:58.5(NV < 35 U/ml)(+) and human chorionic gonadotropin: Negative. 05/31/2017 the patient underwent an exploratory laparotomy and resection of mass: Surgical description Extensive abdominal wall fibrosis, preperitoneal midline mass of firm lobulated consistency of approximately 7×10 cm, adhered to muscle and posterior in relation to dome / anterior bladder wall. Free pelvic cavity. there are no masses, atrophic left ovary, right not visualized. no adenomegalies are evident. Anatomopathological study: Macroscopic: Nodular lesion of violaceous tissue that weighs 136 grams and measures 10×6×5 cm, smooth large surface; internal surface with hard consistency, and areas of necrosis. Microscopic: Fibroadiposous tissue committed by moderately differentiated endometrioid adenocarcinoma, figo2, nuclear degree 2 with focal squamous differentiation. Immunohistochemistry study: Positivity in tumor cells for CX7, PAX 8, RE, RP, VIMENTIN. Negative for CK20, CEA, AE1/AE3, TTF-1, THYLOGLOBULINE AND WT-1. Cell proliferation index measured by KI67 30%. Pathology conclusion: primary origin in endometrium. 08/17/2017. Chest CT: Nonspecific pulmonary nodule in the apicoposterior segment of the left upper lobe. The patient is taken to segmental lobectomy wedge resection of left lung lesion by thoracoscopy. Pathology report:confirms metastatic disease of gynecological origin, with edges of section and pleura compromised by tumor.
Conclusion
Sixty-nine-year-old patient with a history of Hysterectomy 18 years before with metastatic endometrial adenocarcinoma to abdominal wall and lung.

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EP147

From aneuploidy to eyploidy: a spontaneous, uncomplicated pregnancy in a patient with 45X0/47XXX mosaicism

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Turner syndrome (TS) is a chromosomal abnormality, due to a total or partial loss of one of the X chromosomes and is mostly characterized clinically by short stature and primary ovarian insufficiency. Spontaneous pregnancies in TS are rare (5%) and of relatively high risk, due to cardiovascular complications. Therefore, close medical monitoring is required. We report a case of a 21-year old woman with TS that had a full term uncomplicated pregnancy after spontaneous conception, giving birth to a healthy female (46XX) infant. The factors leading to this favorable outcome are discussed.

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EP148

Birth weight of children born to women with AITD compared with those born to women without AITD

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Aim
The aim of the study was to evaluate the birth weight of children born to women with AITD compared to with those born to women without AITD.
Material and methods
The study included 596 pregnant women and their children in 2007–2015. The patients were divided into two groups. The first (group A) consisted of 191 pregnant women with chronic autoimmune thyroiditis and their children, while the second (group B) consisted of 405 pregnant women without this disease and their children. In each woman, the serum levels of anti-TPO and anti-TG were measured during pregnancy. In newborns birth weight was assessed.
Results
In group A, 191 newborns of women with AITD the average birth weight was 3450 g. In group B, 405 newborns of women without AITD the average birth weight was 3300 g.
Conclusion
The occurrence of autoimmune thyroid disease in pregnant women increases birth weight of their children.

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EP149

"Gym and anabolists"

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This is a 38-year-old male, a regular user of a gym with the sole purpose of improving his physical performance and muscular strength and habitual consumer of hyperproteic dietary supplements. Among his PAs he denies toxic habits, and highlights the removal of the right testicle in childhood. Consultation for decreased desire and sexual potency, together with pain and turgor in the left breast; hair loss at the frontal level, in analytic carried out by the Primary Care Physician, the level of Testosterone decreased (0.21 ng/ml) is the normal units, reason for which it is derived to Endocrinology Consultations. In the history acknowledges that from 2005 to 2009 has been a consumer of anabolic (Decarbolin, Sustanol 5HT, Histrol) cyclically and by different routes of administration, with the sole purpose of increasing physical power to exercise, denies such consumption in the last year and a half. In the physical examination gynecomastia draws attention being the rest of the normal exploration. In the complementary study performed, testosterone levels 0.21 ng/dl, with rest of hormonal profile within normality (FSH 1.5 mU/ml, LH 0.7 mU/ml, PRL 17.9 ng/ml, ACTH 20 IU/ml, Basal cortisol 16.40, TSH 2.29 μUI/ml, HCG < 0.05 ng/ml, 17 beta-estradiol 21 pg/ml), high CPK levels. Abdominal, mammary and testicular ultrasound, normal except absence of right testis. Incidentaloma pituitary MRI scan (4 mm). Given the findings of complementary tests and history of consumption of anabolics, hypogonadotropic hypogonadism was diagnosed secondary to taking anabolic steroids, without consumption at present for a year and a half. Testosterone treatment is started, and reviewing literature, there are cases in which patients benefit from adjuvant treatment with human chorionic gonadotrophin (hCG) at doses 500 IU, after testosterone for three months. He has always shown a demanding attitude, questioning the diagnosis, so he asks for a second medical opinion. Anabolic androgenic steroids are synthetic androgens derived from testosterone, widely used in athletes, especially in bodybuilders and athletes of high competition, the administration of doses far superior to physiological induce the appearance of side effects, highlighting alterations in sexual function and reproductive.

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EP150

Amenorrhea and benign intracranial hypertension as an effect of antipsychotic therapy in a patient with schizophrenia

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Introduction
The management of schizophrenia involves drugs which inhibit domapine receptors. The drugs control the disease. However, they increase prolactin secretion and induce amenorrhea. The drugs induce the development of metabolic syndrome and as a result of obesity they may cause benign intracranial hypertension.

Aim
The aim was to describe the case of a patient who developed schizophrenia and after therapy with antipsychotics benign intracranial hypertension and amenorrhea.
Case description
A patient, female, aged 21, developed schizophrenia. After diagnosis treatment with antipsychotic medication was initiated. Antipsychotic treatment induced obesity and subsequently benign intracranial hypertension. Benign intracranial hypertension reduced her visual acuity and induced hearing loss within a year. Acetazolamide was administered for the control of intracranial hypertension. The patient also developed amenorrhea. Prolactin was 150 ng/ml (normal range 2–29 ng/ml). Cabergoline was administered for the management of hyperprolactinemia.
Conclusion
Antipsychotic treatment for the management of schizophrenia may be accompanied by the development of obesity and in some cases benign intracranial hypertension. Benign intracranial hypertension, despite its name, may have severe consequences such as reduction of visual acuity and hearing loss, being, according to the literature "not so benign". Amenorrhea affects health and quality of life in a young female patient. The use of the new atypical antipsychotics may be a solution for the prevention of the serious adverse effects of antipsychotic treatment, such as benign intracranial hypertension and amenorrhea.

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EP151

Hirsutism in patients with polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is a heterogeneous disorder, characterized by chronic anovulation and hyperandrogenism. Hirsutism, defined as excessive terminal hair that appears in a male pattern in a woman, is frequently present in patients with PCOS. We aimed to determine the clinical and biological characteristics of hirsute patients with PCOS.
Methods
It was a retrospective study included 30 women diagnosed with PCOS according to the Rotterdam consensus. Hirsutism was defined as a Ferriman–Gallwey score ≥ 8. The medical history, physical examination findings and hormonal profiles were documented and analyzed.
Results
The mean age of the study population was 27.7 ± 8.4 years. A family history of hypertension and diabetes was found in 73% of cases. Hirsutism occured in puberty in 80% of cases. It was severe in only one woman (3%) and mild to moderate in 29 women (97%). Menstrual abnormalities were present in 22 women (73%) and 4 women (13%) had a history of miscarriage. The remainder of the clinical examination revealed the presence of acne, acanthosis nigricans, android obesity and hypertension in 17%, 30%, 70% and 16% of cases, respectively. Hormonal assessment showed hyperandrogenism in 70% of patients with a mean level of testosterone of 0.9 ± 0.4 ng/ml and moderate hyperprolactinemia in 3 cases (10%). Metabolic exploration found a glucose intolerance, diabetes and hypertriglyceridemia in 10%, 13% and 13% of patients, respectively. The prevalence of metabolic syndrome was 36.7%.
Conclusion
In patients with PCOS, hirsutism is often mild to moderate with a progressive onset and without other signs of virilization. The association with metabolic disorders is frequent, highlighting the contribution of insulin resistance in the pathophysiology of PCOS.

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EP152

Evolution of premature ovarian failure after 15 years of follow-up

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Introduction
The therapeutic management of premature ovarian failure (POF) consists of a hormone replacement therapy that must be regular to avoid cardiovascular and bone complications as well as psychological management. The objective of this work was to study complications at 15 years of evolution of 42 tunisian women followed for POF.
Patients and methods
It's a retrospective study of 42 patients followed in the endocrinology department of Sousse for POF between 2000 and 2017.
Results
The average age of the patients was 23.85 years old. All patients were treated with combined estrogen/progestin hormone replacement therapy with a sequential regimen in 11 patients to ensure withdrawal bleeding. After 15 years of follow-up on average, a final small height was found in 5 patients with an average height of 147.85 cm. The average body mass index was 24.51 kg/m^2. The average waist circumference was 90,5 cm. Three patients became diabetic, one patient was followed for hypertension and one patient was followed for dyslipidemia. Metabolic syndrome criteria were met in one third of patients. No patient had a cardiovascular event. Bone densitometry showed osteoporosis in 21.43% of patients and osteopenia in 35.71% of patients. Two patients had pathological fracture at the age of 28 and 39, respectively. Therapeutic non-compliance of hormone replacement therapy was observed in 20% of patients.
Conclusion
The two major risks of hypoestrogenism secondary to POF are cardiovascular risk and bone risk. If the patient is substituted, these risks should be avoided. However, few studies have prospectively evaluated the effects of estrogen therapy on cardiovascular risk in patients with POF.

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EP153

Diagnostic difficulties in precocious puberty

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Introduction
Precocious puberty (PP) is the development of secondary sexual characteristics before the age of 8 years in girls and beforethe age of 9 years in boys. Central PP has an idiopathic origin in upto 95% of girls while in up to 50% of males. The diagnostic and the management of PP can beparticularly complex. Here we describe cases of two sisters having central PP with different presentation and evolution.
Observations
First case: A 13-years-old female diagnosed at the age of 6 years and a half with central PP. She presented anaccelerated linear growth with an initial height equal to 126 cm/+3SD, Tanner stage 3 and advanced bone age by 3 years and a half. Basal LH level was high at 2.5 mIU/mL which was multiplied by 14 after GnRH administration, estradiol was 12 pg/mL. Brain Imaging was normal. She received GnRH agonist therapy during 3 years and a half with a final height of 155 cm. Second case: Her little sister aged of 10-years 3 months was followed-up from the age of 4 years and a half. Her initial height was 104 cm/-1SD,Tanner stage 2 and she had an advanced bone age by 1 year. Basal LH and FSH was respectively 1.2 and 2 mIU/mL and its peak concentrations after GnRH agonist stimulation was respectively 6.5 and 12 mIU/mL. Brainimaging was normal. The decision was to follow-up the patient. During her irregular follow-up, she experienced an accelerated growth rate of 16 cm between the age of 7-9 years followed by a gain of only 1 cmin the year after. Menarche occurred at the age of 10 years, her height was 137 cm VS target height of 147 cm.
Conclusion
The management of PP has several challenges especially distinguishing normal from pathologicalpubertal development, achieving normal adult height and avoiding its psychosocial consequences.

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EP154

Mayer-Rokitansky-Kuster-Hauser syndrome type II

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The normal development of the female reproductive tract depends on the interaction between genetic, hormonal and environmental factors for the differentiation of the Müller and Wolff ducts, and the urogenital sinus
Case report
16-year-old female, single, school student presented to our endocrine department complaining of primary amenorrhea. No history of chronic diseases, excessive exercise,medications, anorexia, clinical hypothyroidism or hyperandrogenism. Family history revealed positive consanguinity. Mother menarche at age 11, her elder sister diagnosed as turner syndrome [45xo] with infantile uterus and both ovaries are not visualized. Physical examination: weight 61kg, height:170 cm BMI: 21.1. Female phenotype, Tanner classification: breasts (4) axillary hair (2), pubic hair (2). Genital examination rudimentary clitoris, unchanged inner and outer labia grooved urethra with elevated edges. Laboratory work up showed follicle-stimulating hormone: 5.35 mIU/ml (N: 0.7–11.1). Luteinizing hormone: 8.1 mIU/ml (N: 0.8–7.6). Pelvi abdominal ultrasonography showing midline solitary pelvic kidney, absent uterus,visible rt ovary measuring 23×15 mm,visible lt ovary measuring 23×22 mm. Genetic evaluation revealed karyotype 46,XX, thus determining the diagnosis of Mayer-Rokitansky-Kuster-Hauser syndrome. Type II
Conclusion
Mayer-Rokitansky syndrome generates anxiety and psychological distress with consequences on the patient's quality of life, thus requiring a multidisciplinary approach

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EP156

Pituitary hyperplasia secondary to congenital primary hypothyroidism in adult patient

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Introduction
The reactive pituitary gland enlargement is a non-neoplastic growth of at least one pituitary lineage, which can often be essential or secondary to prolonged deficit of a gland target. It may be difficult to differentiate from functional pituitary adenomas. Herein we report a case of pituitary hyperplasia secondary to congenital primary hypothyroidism diagnosed at the age of 38 years.
Observation
A 38-year-old female patient presented with spaniomenorrhea, mental retardation and delayed stature. On physical examination,she had a height of 134 cm, a weight of 54 kg, adult pubertal status, galactorrhea, skin infiltration and non-palpable thyroid gland. Her hormonal profile showed raised thyrotropin stimulating hormone (TSH) (>100 mIU/L, range: 0.35-5), low FT4 (<0.40 ng/dL, range: 0.7-1.5) and hyperprolactinemia (142 µg/L). Further investigation showed negative antiperoxydase antibodies and the scintigraphy confirmed an ectopic sublingual thyroid gland. The patient was put on levothyroxine replacement therapy. Four months later, she presented with a normal TSH level but a persistent hyperprolactinemia (69 µg/L). A pituitary magnetic resonance imaging (MRI), requested in order to explore this hyperprolactinemia, showed diffuse pituitary enlargement with stalk deviation.
Conclusion
In our review of the literature, primary uncontrolled hypothyroidism has been described as a precursor to pituitary hyperplasia. It results from the loss of thyroxine feedback inhibition and the subsequent overproduction of thyrotropin-releasing hormone (TRH). L-thyroxine replacement therapy prevents enlargement of pituitary gland and may regress the change, but is not the only outcome of pituitary enlargement. Other coexisting disturbances must be considered when the treatment is not successful.

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Thyroid

EP155

Thyroid disease in very elderly patients

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Objective
To know characteristics of patients older than 80 years with thyroid disease.
Patients and methods
Prospective 6-month study in which we analyze characteristics of patients that have been treated and followed for thyroid disease in endocrinology consult.
Results
Hundred and fifteen patients were analyzed of them, 23 men and 92 women, with 83.78±2.12 years-old. Comorbidities. Arterial hypertension 53%, previous neoplasms 18%, CHF15%, COPD 11%, cognitive impairment 11%, stroke 8%, ischemic heart disease 8%, chronic renal failure 6%. Thyroid pathologies were: hyperthyroidism 29% euthyroid goiters 28%, hypothyroidism 16%, subclinical hyperthyroidism 13%, thyroid cancer 6%, subclinical hypothyroidism 4%, amiodarone thyroiditis 4%. Study and treatment used was similar to patients under 80 year-old, multinodular goiter was the most frequently cause of hyperthyroidism. Metabolic pathologies associated: dyslipidemia 35%, type 2 diabetes mellitus 30%, osteoporosis 19%, hyperuricemia 10%, obesity 7%, hypoparathyroidism secondary to surgery 4%.
Discussion
The most common form of thyroid dysfunction in the elderly is subclinical hypothyroidism occurring up to 15%. In our study was hyperthyroidism, possibly due that subclinical hypothyroidism was controlled from primary care. Prevalence of hyperthyroidism in elderly ranges from 0.5 to 2.3%.The most frequents causes were toxic multinodular goiter, Graves' disease, toxic adenoma. Subclinical hyperthyroidism may be present in up to 2%.
Conclusions
The prevalence of thyroid disease in elderly is higher than the general population and is associated with significant morbidity. Usually in the elderly healthy population there is a high rate of thyroid dysfunctions that are not detected. Dyslipidemia and diabetes mellitus were the main associated endocrine pathologies.

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EP157

Beyond conventional hyperthyroidism: a rare association of inflammatory bowel disease and inflammatory myopathy with Grave's disease

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Introduction
Graves' disease being one of the common cause of hyperthyroidism and thyrotoxicosis at presentation, is actually caused by an antibody directed to TSH receptor which leads to hyper functioning of the gland. Being an autoimmuno disease, it may be associated with other autoimmuno diseases. Inflammatory myopathy like polymyositis is less frequently observed in patient with Graves and inflammatory bowel disease again is infrequent as per as the association is concern. Association of inflammatory myopathy and inflammatory bowel disease in a single patient of Grave's disease is rare and poses a significant diagnostic and therapeutic problem.
Case study
A 51 years menopausal woman presented to outpatient department of IPGMER with history of shortness of breath, palpitation, bilateral lower limb swelling for one month and Jaundice for last 15 days. She was also complaining of swelling of her neck for last six months and episodic large volume diarrhoea with occasional blood mixed stool for last eight months. She was apparently well until six months prior when she noticed gradually progressive neck swelling. Clinical and Biochemical evaluation imparted that she was having thyrotoxicosis with congestive cardiac failure and jaundice. Thyroid evaluation showed she was having diffuse goitre. She had Anti TPO and Anti TSH receptor antibody high positive. A diagnosis of graves presented with thyrotoxicosis was made. She was salvaged conservatively with thyroid suppression and beta blocker. On the day 4th of admission when she was recovering from the thyrotoxic crisis she developed severe proximal muscle weakness with power or 2/5 in both lower limbs and 3/5 in both upper limbs with preservation of jerks, normal tone and sensory and autonomic functions. EMG study showed myopathic pattern and biopsy proved

that as polymyositis. Diarrhoea was persisting and history of prolong episodic bloody stool lead us to go for a colonoscopy and guided biopsy. Lesion was consistent with Crohn's disease. We have made our final diagnosis as Grave's disease presented with thyrotoxicosis having an associated inflammatory myopathy with inflammatory bowel disease. Steroid was added with pre administered regime and patient symptomatically improved.
Discussion
This case illustrate a rare association of Grave's disease with polymyositis and Crohn's disease. Mimicar, thyroid myopthy may suppress inflammatory myopathy and diarrhoea itself can be a feature of thyrotoxicosis.There is scarcity of cases shown association among these three autoimmunidiseases. Recognition of this condition is essential as per as proper therapy is concern.

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EP158

What should be the cut-off level for antithyroperoxydase antibody? January 2018

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Aim
The biological diagnostic of Hashimoto thyroiditis (HT) is based on higher than normal levels of antithyroperoxydase antibodies (ATPO). Our goal was to establish the cut-off limit of normality (the upper limit) for ATPO in our thyroid normal patients. This limit, and not that of the laboratory, should be used as diagnosis of Hashimoto thyroiditis.
Material and method
1. ATPO was investigated in patients with normal level of thyroid hormones (euthyroidism) and normal ultrasound of thyroid (linear probe at 7.5–10 MHz). 2. ATPO was analyzed in several Bucharest laboratories, accredited for this investigation. The laboratory cut-off limit for normality was 34 ui/ml. 3. Conventionally, the normality is considered as the average (mean) plus/minus standard deviation multiply by 2.
Results
A. Patients: 404; women - 328 (77%), men – 76 (23%); age: average - 44.6, median - 42; average TSH: 1.84 mui/ml, FT4, 15 nmol/l. B. ATPO level was: average: 8.65 ui/ml, standard deviation: 6.88. Therefore, the upper limit should be 21.89 ui/ml.
Discussion
Based on 34 ui/ml cut-off limit, we registered 1750 patients with HT (higher ATPO), 205 patients with only high antithyroglobuline thyroiditis (ATG-T) (low ATPO), 126 patients with idiopathic myxedema (hypothyroidism, lower ATPO/ATG, and inflammatory ultrasound signs) and 1875 patients control, with other thyroid diseases (mostly thyroid nodules). Considering ATPO cut-off as 21.89 ui/ml, 29 patients with ATG-T (14.15%) and 12 patients with idiopathic myxedema (9.52%) should be considered, in fact, HT patients. Moreover, 135 control patients (7.19%) with ultrasound inflammatory signs should be considered HT patients, too.
Conclusions
1. Using the data from our patients, the cut-off limit for ATPO should be 21.89 ui/ml and not 34 ui/ml. 2. Based on 23 ui/ml cut-off limit, the number of patients with Hashimoto thyroiditis increased by 10.3%. 3. Every research group should establish its specific cut off for ATPO level.

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EP159

Total thyroidectomy can be a radical method of treatment of Grave's disease in alcohol addicted patient who has hepatitis B at the same time, because medical treatment can aggrivate liver disease and bring to recurrence of Grave's disease

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34 years old male patient was admitted to Endocrine department with palpitation (130–140 beats/minute), weight loss(15 kg during 3 months), anxiety, nervousness, hand tremor, generalized nocturnal pruritus. Laboratory examination showed: decreased level of thyroid stimulating hormone (TSH) <0.005 (n 0.3–4.0 iu/ml), markedly increased level of free thyroxin (FT4) - 100(n 12–22 pmol/l), free triiodthryonine FT3-6,5 (n-0,8-2,0 ng/ml),anti-R-TSH 15-(n- $<$ 1,75T, Anti –TPO 1000,0 (n-$>$34). Glucose and other blood tests ALAT, ASAT,creatinine, ammonia were within normal range.Thyroid ultrasound showed bilaterally enlarged gland with volume of 50 ml, without nodules. Presence of $\ll$ thyroid inferno $\gg$. Patient was diagnosed Grave's thyrotoxicosis. Follow up after 3 weeks of treatment with Thyrazol 50 mg per day, Anaprilin 160 mg 4 times per day, Mirtazapine 7,5 mg showed:weight gain 5 kg, pulse 90–100 beats/minute, absence of nocturnal pruritus after Miratzapine. Laboratory follow up: FT4 40,0, (n-12–22 pmol/l)T3 4,5 ng/ml(n-0,8-2,0 ng/ml). Treatment continued with same daily dose of Thyrazol and Anaprilin 120 mg.Mirtazapine canceled. After 4 weeks patient had weight loss 2,5 kg, palpitation 110–120 beats/minute, abdominal pain, diarrhea, jaundice. Abdominal ultrasonography showed few small calcifications on the right lobe of liver. Laboratory follow up showed increased (AlAT)150 U/l, increased Total Bilirubin 2,5(n-0,2-1,2 mg/dl) and elevated FT4() -105 pmol/l. Hepatitis are checked: Hepatitis C and A were negative.HBsAg 1081,55 S/CO. HBV quantitative 108 IU/ml. It appeared patient had teeth removal one year ago. After consultation with infectionsit anti viral treatment didn't prescribed. Taiking in account presence of hepatitis B, alcoholism, hepatotoxicity of Thyrazol, heigh level of anti-R TSH, Thyrazol canceled and patient prepared for total thyroidectomy as Radioiodine therapy is unavailable in Armenia.Patient was given lyugol solution for 10 day 7 dropss per day and b –blocker.After 10 day FT4 became 24 pmol/l (n-12-22 pmol/l), Ft3 1,9-(n–0,8-2,0 ng/ml) L. Patient underwent total thyroidectomy than prescribed replacement therapy with L- Thyroxin. One month after FT4- 15 pmol/l, TSH 1,5 IU/ML, ALAT-35 U/I, Total Bilirubin 0,9 mg/dl. Hepatitis markers were within same ranges. Patient's condition has improved.
Conclusion
Medical treatment of Grave's disease with presence of Hepatitis B, high level of Anti R-TSH and alcohol addiction can not only aggravate liver disease but bring to recurrence of Grave's disease.Total thyroidectomy can be a method of chose in this case.

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EP160

The complications of diseases of thyroid gland at children and teenagers according to data for 5 years

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The aim
To study the complications of diseases of thyroid gland at children and teenagers according to data for 5 years.
Material and methods of investigation
Under supervision of the employees of the department of children's endocrinology the Center of Endocrinology of PH of RUz during from 2012 on 2016 years was hospitalized 213 children and teenagers with various diseases of thyroid gland, from them of the boys was - 67 (31,4%), girls -146 (68,5%). 20 sound children and the teenagers of the appropriate age made the group of the control.
Results
The most of patients were in teenager age, namely from 11 to 17 years - 147 patients (69,1%), were at the same time mostly sick girl - 100 from 147 (68,0%). At our patients the manifest hypothyroidism was marked, that is authentic increase in TSH against the background of authentic lowering of the free thyroxin of blood on a comparison with group of monitoring was watched. According to our data, children and teenagers had the following frequency of complications of the main diseases: delay of skeletal development – 17,8%, delay of physical, sexual, mental, speech development – 25,8%, delay of physical, mental development – 20,4%, delay of physical, sexual development – 15,6%, delay of physical development – 14,5%.
Conclusions
The researches conducted by us allowed to estimate gravity of the goiter endemiya and expressiveness of manifestations of violation of sexual and physical development. The results received by us confirm need of further long observation and treatment of patients.

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EP161

A TSH pituitary adenoma due to Hashimoto Thyroiditis and L-tiriiodotironin treatment experience: Case report

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Aim
We report a child with reactive pituitary enlargement and microadenoma due to Hashimoto thyroiditis.We want to emphasize the importance of good endocrine evaluation in pediatric cases of pituitary adenomas
Case report
A 7 year 7 month old boy presented with mild symptoms of hypothyroidism. There was no feature in his past medical story.He had normal cognitive and neurological development. At physical examination his weight was 24 kg (0.06 SDS) and height was 122.5 cm (−0.20 SDS). His systemic evaluation was normal. In hormonal workup low free thyroxine (0.75 ng/dl) (0.82–1.62),low tiriiodotironin (0.99 pg/ml) (2.73–4.92) and high TSH (>150 mIU/ml)(0.8–5.4) levels, and hyperprolactinemia (prolactin level at 36.33 mIU/l), TSH reseptor antibody was 0.49, TGAb (>3000 mIU/ml), TMAb (>1000 mIU/ml) were obtained.. In ultrasonography thyroid gland was larger and heterogeneous images were seen. Hashimoto thyroiditis were diagnosed and Levotiroksin treatment (3 mcg/kg/g) was started and gradually increased.In follow up TSH was not suprese despite free t4 rise. Macro TSH was negative.Pituitary imaging was performed. The height of the pituitary was measured as 11.5 mm. It creates a slight pressure on the optical chiasm. Within the pituitary, there is a region of 6×9 mm in diameter with low contrast.It was reported as microadenoma. Then treatment was planned as L-tiriiodotironin (12.5 mcg/day) and dose adjustment done according to hormone levels.After 1 month in pituitary imaging, the height of the pituitary was measured as 6.6 mm,staining was homogeneous and no mass was seen. TSH level was depressed. (TSH: 47.64 mIU/ml, FT4: 1.15 ng/dl). The patient's treatment and follow-up continues
Conclusion
Based on the clinical and laboratory data a diagnosis of pituitary microadenoma secondary to chronic autoimmune thyroiditis was made. Primary hypothyroidism should be considered in the differential diagnosis of pituitary masses

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EP162

Expectant management in patients with multinodular goiter: expected development options

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Today dynamic observation are given preference in most cases multinodular goiter. Small nodes without disruption of thyroid function do not affect the quality of life of patients. Wait-and-see tactic with multinodular goiter has previously been submitted due to the lack of adequate replacement therapy. Wait-and-see tactic previously criticized because of its passivity and predictable negative effect on growth nodes. The result of passive observation is the occurrence of goiters of large size that patients are treated as a minor inconvenience. A retrospective investigation of multinodular goiter large size was made. Over 8 years of experience in the operational treatment were 2519 patients with various thyroid disease (women, 2194, men - 325). Of the total number of patients, we selected 34 cases (1.35%) multinodular goiters. The inclusion criteria in the study were: i) the presence of multiple nodes in thyroid, ii) the mass of the removed thyroid tissue 200 g or more, iii) pathological confirmation of focal lesions of thyroid (macro-microfollicular colloid goiter, thyroid adenoma, thyroid cancer). Assessed clinical and instrumental diagnostic methods in the evaluation of the severity of the changes in the thyroid gland in this disease. Describes the features of performing operations in patients with large multinodular goiters. Presents a clinical case illustrating features of the development, diagnosis, surgical treatment and postoperative rehabilitation of patients with thyroid cancer arising in the background of a giant multinodular goiter. Today there is no clear clinical criteria of the syndrome of compression that would allow to set the indications for surgery. The subjective assessment of well-being, fear of surgery prevent patients adequately assess the effects of high thyroid in human health. The necessary precise regulation of the stages of the monitoring, a must for doctors and patients, as well as an emphasis on instrumental methods in the evaluation of thyroid growing. It is proved that dynamic monitoring in multinodular goiter effective only when adequate monitoring of patients, and with pronounced negative dynamics must be indications for surgery. Among instrumental diagnostic methods the most informative has the x-ray computed tomography.

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EP163

The effects of vitamin D supplementation on insulin resistance in patients with hypothyroidism

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Background
Over the past decade, numerous non-skeletal diseases have been reported to be associated with vitamin D deficiency including autoimmune thyroid pathology.
Aim
The aim of the study is to evaluate the effects of vitamin D supplementation on insulin resistance in hypothyroidism.
Materials and methods
Forty-seven participants, 32–74 years old, including 39 women (82.9%) and 8 men (17.1%) took part in the study. Serum TSH, insulin and 25(OH)D concentration were measured, and HOMA-IR was calculated. All measurements were performed at the beginning and the end of the study. Patients with hypothyroidism received 21,000 unit of cholecalciferol orally per week for 12 weeks. The results were analyzed by descriptive tests, and a comparison between variables were made using paired *T*-tests or Wilcoxon tests, as a appropriate.
Results
All of the participants were vitamin D deficient. Mean serum 25(OH)D concentration was 21.72±6.14 ng/ml. The results at baseline and at the end were for insulin 19.36±2.39 and 9.92±2.38 mIU/l ($P<0.05$) and for HOMA-IR, 3.91±0.32 and 2.38±0.17 ($P<0.05$) respectively.
Conclusions
Our data showed significant improvement in serum insulin and in HOMA-IR after treatment with cholecalciferol, suggested that vitamin D supplementation could reduce insulin resistance in hypothyroidism.

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EP164

Clinical and morphological characteristics of the first time nodular goiter

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We analyzed the results of a survey of 51 patients aged 18 to 25 years who were not exposed to ^{131}**I**. Patients included in the study had a the first time nodular goiter. The median age of the patient at the time of the diagnosis of nodular goiter was 22.00 (20.32; 23.21) years. Male/female ratio was 1/16. In 23.5% of patients the site was formed against the background of autoimmune thyroiditis, in 76.5% the true nodal formations were revealed against the background of the normal ultrasound structure of the thyroid gland. The sizes of the revealed nodes were in the range of 0.7–1.5 cm. One-half of those surveyed in the thyroid gland were lysed with isoechoic nodes, about 10% of which had ultrasound signs of cystic degeneration. The median free T_4 level was 14.72 (13.25, 16.83) nmol/l, TSH - 1.56 (1.01, 2.23) MmE/l and corresponded to the range of reference values. More than 50% of those surveyed had indications for a fine needle aspiration biopsy. Based on the results of the cytological examination, benign changes were detected in the nodal formations with different degrees of proliferation of the thyroid epithelium. About 10% of those surveyed had cytological signs of degenerative node changes. In 7 (13.7%) of the patients examined, there was a suspicion of papillary cancer. The cytological conclusion was confirmed in all cases after the histological examination. In young adults, benign forms of nodular goiter prevail against the background of a normal thyroid status. However, sporadic cases of thyroid cancer are recorded.

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EP165

Thyrotoxic vomiting: an unusual presentation

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Introduction
Thyrotoxicosis classically presents with tremor, goitre, sweating and diarrhoea. It is increasingly appreciated, however, that presentations can be complex and non-specific. Gastrointestinal symptoms in thyrotoxicosis are thought to derive from increased motility. Thyroid overactivity may be a cause for unexplained repeated vomiting and abdominal pain.
Case
A case of 41-year-old man presented with a three-year history of intractable vomiting, intermittent abdominal pain, sweating, hiccups, and 20 kg weight loss. He previously had surgical laparotomy to correct malrotation that had been found on CT scan at his local hospital. The malrotation was thought to be the cause of his symptoms. However, surgery did not lead to symptomatic relief, and caused complications in the form of poor wound healing and infection. He was then commenced on Sertraline for anxiety that was attributed to multiple hospital admissions and invasive investigations over three years. He was referred over to our unit for further investigations. A repeat CT showed that the malrotation had not been fully corrected, but that there was no sign of obstruction. It was agreed that the malrotation was probably an incidental finding. A marked tachycardia and hypertension were noted at this point, but attributed, along with pyrexia, to infection with Clostridium difficile. Other differential diagnoses were considered and more tests ordered, including: a porphyria screen, C4 levels, serum lead, faecal calprotectin, C1 esterase and a specific test for Familial Mediterranean Fever. Moreover, imaging was scheduled: MRCP, a gastric emptying study, endoscopic ultrasound and, CT head. Towards the latter part of his admission, he noticed a swelling in his neck. One month later, thyroid function blood tests were ordered; these showed a TSH $<$0.03 mU/l (0.35–5.5) and T4 55.9 pmol (10–19.8). TRAB antibody was positive. He was diagnosed with Grave's disease. The vomiting and epigastric pain remarkably improved following treatment with Carbimazole.
Discussion
Whilst uncommon, thyrotoxicosis should be considered in patients with persistent, unexplained vomiting. Thyroid function tests should be checked so as to avoid delays in diagnosis and potentially obviate the need for invasive and non invasive tests and procedures, allowing the initiation of treatment as early as possible.

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EP166

Thyrotoxic periodic paralysis: a rare complication of hyperthyroidism for 21-year-old male.

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Introduction
Thyrotoxic periodic paralysis (TPP) is very rare (prevalence in non-Asian populations 0.1–0.2%, more frequent in men) and potentially life-threatening complication of hyperthyroidism. TPP develops when thyroid hormones cause sodium-potassium-adenosine triphosphatase (Na/K-ATPase) pump overactivity, leading to rapid potassium shift into the cells resulting in hypokalaemia. This causes transient episode of muscular weakness usually involving lower limbs and hypokalaemia, sometimes - respiratory weakness and severe, even fatal arrhythmias. TPP usually presents early in the morning, after heavy unusual exercise, stress or a high carbohydrate intake. Diagnosis is difficult because of the rarity and subtlety of symptoms.
Case presentation
A 21-year-old male was admitted to the emergency room with tetraplegia, which gradually developed for about 24 hours and was provoked by unusually vigorous physical activity. First it was hard to climb the stairs and in 12 hours – he woke up in the morning and couldn't move. On physical examination: BMI–28.7 kg/m^2, HR 93beats/minute, BP 125/60 mmHg. Thyroid non-palpable. Weakness of all limbs with power 1-2/5. No other neurological changes were found. Laboratory analyses: chemistry panel and complete blood count was all normal, except of serum potassium of 1.8 mmol/l. Instrumental analyses: Head CT scan – no acute pathology was found. ECG-sinus tachycardia- HR 97beats/minute and U waves. After acute treatment with intravenous potassium supplements (KCl 10%60 ml per 12 h), muscle weakness disappeared, serum K raised to 5.8 mmol/l and patient was moved to endocrinology department. Revised medical history: excessive sweating, heat intolerance for about 1 month. Physical examination showed normal power of all limbs (5/5). Laboratory analyses: K– 4.5 mmol/l. 24 hour urine: K–58.5 mmol/24 h (*n*.38–125 mmol/24 h). Prolactin–248.0 mU/l (*n*.72.6–407.4), Aldosterone–211.92 ng/l (*n*.13.3–231.4), ACTH–22.7 ng/l (*n*. $<$46). TTH–0.001 mU/l (*n*.0.4–4.0), FT4–31.14 pmol/l (*n*.9.0–19.0), FT3–16.53 pmol/l (*n*.2.61–7.70). Thyroid ultrasound – diffuse nodular goiter. Clinical diagnosis: Diffuse nodular goiter, hyperthyroidism. Thyrotoxic periodical paralysis. Hypokalaemia. Treatment: Thiamazoli 30mg daily, with down-titration, after 10days. After 1 month of recommended treatment, muscle weakness episodes didn't recur, excessive sweating, heat intolerance diminished, potassium concentration and thyroid hormones were normal K-4.7 mmol/l, FT4 – 15.07 pmol/l, FT3 – 6.35 pmol/l.
Conclusion
TTP is potentially lethal condition, which is difficult to diagnose, thus for all patients with unclear ethology of paralysis, thyroid hormones should be tested. All efforts should be used to achieve euthyroidism as early as possible, because it's the only way to avoid TPP.

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EP167

Graves disease, pericarditis and thymus hyperplasia: the improbable triad!

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Introduction
Ophthalmopathy and dermatopathy are the most frequent manifestations of Graves Disease (GD). It is also known the relation between GD and other autoimmune diseases like myasthenia gravis. Thymus hyperplasia in GD is already documented on literature but it's mechanism is not well understood. There are two possible explanations, one related to thyrotrophin receptors stimulation present on thymus, and other related to tissue stimulation due to generalized hyperplasia from lymphoid system. On the other hand, the association between hyperthyroidism and pericarditis, although rare, has been described before. However, aetiology remains unknown. There is only one case reported, describing the association between GD, pericarditis and thymus hyperplasia.
Clinical Case
22 years old, healthy man attended endocrinology department at February 2017 with symptoms of hyperthyroidism. Laboratory evaluation revealed TSH $<$ 0.1 mUI/l (0.45–4.5mUI/l), FT4 3.87 ng/dl (0.79–1.76 ng/dl), anti-thyroid peroxidase antibodies 663 UI/l and anti-thyrotropin receptor antibodies (TRABs) 15.6 UI/l (both positive), and anti-acethylcholine antibodies were negative. After diagnosis of hyperthyroidism, he started therapy with methimazole and propanolol. Five months later, he was admitted at the ER, complaining from fever and pre-cordial pain. The electrocardiogram showed acute pericarditis, although without effusion or suggestive image on the echocardiogram, reason why he performed a TC scan. TC revealed an anterior homogeneous mediastinum mass with 39$\times$20 mm, compatible with thymus hyperplasia. After observation by a cardio-thoracic surgeon, he had indication to maintain GD therapy and imaging re-evaluation in 3 months.
Discussion
This case reveals a coexistence of pericarditis and thymus hyperplasia in a patient with GD. In the presence of mediastinum mass with benign features (homogeneous mass, defined outlines, without calcifications and without invasion of fat or pleura nor cystic component) and if concomitant GD, the hypothesis of thymus hyperplasia should prevail. It is also known the regression of thymus volume during hyperthyroidism treatment. Therefore, in the presence of a benign criteria mediastinum mass, invasive diagnostic exams should be delayed while hyperthyroidism treatment is under way, however, imaging control of the mass should be maintained. Rare cases exist reporting pericarditis as a severe hyperthyroidism complication and therefore, its aetiology remains unexplained. The relation between pericarditis and thymus hyperplasia, also described, may be due to, proximity of the hyperplasic thymus tissue to the moving pericardium, resulting in inflammation. The nature and the comprehension of the coexistence of these three entities described, remains unknown, lacking more similar clinical cases for their understanding.

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EP168

Familial dysalbuminaemic hyperthyroxinaemia, a thyroid conundrum

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Background
Familial dysalbuminaemic hyperthyroxinaemia (FDH) is an interesting autosomal dominant condition that is associated with euthyroid hyperthyroxinaemia, whereby patients remain euthyroid but laboratory value will show high free thyroxine (fT_4) level. It is caused by mutations in *ALB* (albumin) gene that increase affinity of albumin for thyroxine (T_4). The usual thyroid assay will show a spuriously high level of thyroxine. This interference could be excluded when the free hormone is extracted from serum and analysed separately. We present a case of a Caucasian lady who was referred to endocrinology team for deranged thyroid function test.
Case
A 50-year-old lady with polycystic ovarian syndrome presents with elevated fT_4, 30.4 pmol/l and triiodothyronine (T_3) level of 5.5 pmol/l with a normal thyroid stimulating hormone (TSH), 4.47 mU/l. Symptoms on presentation include one month history of hot flushes, palpitations and lethargy. Examination findings revealed normal thyroid gland. US thyroid and thyroid uptake scan were unremarkable. Her TSH receptor and thyroid peroxidase antibodies were negative. Her maternal aunt has suffered from thyroid disorders. She was commenced on carbimazole 15 mg once a day. TSH level went up to 6.69 with a T_4 level of 23 and T_3 level of 5.5. She continued to have palpitations and anxiety. Her carbimazole was further increased to 20 mg. Her repeat blood test then showed a TSH and fT_4 of 9.42 and 22. Her case was discussed with Cambridge team who suggested TRH stimulation tests and MR pituitary which were normal. In the meanwhile patient was advised to take alternating dose of carbimazole 20 and 25 mg. Her symptoms remained the same throughout. We sent her blood sample to Cambridge for FDH testing. DELFIA assay in Cambridge showed TSH 3.85 and T_4 19.3. Genetic testing at Cambridge showed a positive mutation in the albumin gene, R242H in keeping with FDH. We stopped carbimazole and commenced propranolol for anxiety. Her repeat results show TSH 3.28 and T_4 26.8 with our laboratory values but normal values with DALFIA analyser.
Conclusion
Euthyroid hyperthyroxinemia is a common condition with several causes. Although rare, FDH should always be one of the differentials. When there is mismatch between the clinical picture and biochemical results, we should establish possible differentials and resist the temptation to treat high free thyroxine as this could potentially lead to unpleasant consequences. It is also important to screen the immediate family members of FDH to avoid unnecessary treatment in similar individuals.

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EP169

Two cases of Graves dermopathy: A rare and pathognomonic symptom

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Introduction
Pretibial myxedema is a rare manifestation of Graves' disease caused by local autoimmune attack of the connective tissue probably mediated by anti TSH receptor autoantibodies (TRab). Its prevalence changes between 0.4 and 5% in Graves 'patients and usually is accompanied by opthalmopathy. The diagnosis requires physical examination and clinical suspicion and in doubtful cases biopsy may be performed.
Case 1
Sixty four years old female patient who has been taking methimazole treatment with the diagnosis of Graves' disease for eight months came to the endocrinology clinic with the complaint of a lesion on the anterior face of lower third of right leg. At the dermatological examination, a plaque with a shiny surface, measuring five centimeters, looking like an orange peel was observed. Upon palpation, it presented a firm and non-depressible consistency. Patient had a history of active moderate orbitopathy and received iv steroid therapy (4.5 gr prednisolone in divided doses). The patient was euthyroid at the time of evaluation with methimazole 2 tb/day and Trab was 1.3 IU/l (at the time of diagnosis it was 135 IU/l). Histopathological incisional biopsy was performed and histopathology revealed accumulation of mucin in reticular dermis leading to separation of collagen bundles. Dermopathy was successfully treated topical corticosteroids.
Case 2
Thirty seven years old female patient admitted to the clinics with symptoms of palpitations, excessive sweating and weight loss. She was diagnosed to have Graves' disease. Radioactive iodine uptake of the thyroid was increased and TRab was three times higher than the upper limit of normal range. She had reddish edema on the distal tibia and was referred to the dermatology clinics. Pretibial myxedema diagnosis was made clinically and the lesion disappeared completely with topical steroids.
Conclusion
Graves' dermopathy is typically asymptomatic, they are rarely pruritic or painful. In severe cases, associated with acropathy, bone pain may result from an underlying periosteal reaction. In patients with high TRab levels and orbitopathy, we should make a proper physical examination and refer the patient to a dermatologist if the patients has a lesion and the diagnosis is equivocal.

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EP170

BsmI, TaqI, ApaI and FokI VDR polymorphism in women wit and without goiter

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Objective
Vitamin D deficiency is common in polish population and seem to play role in pathogenesis of some diseases. We looked for correlation between polymorphisms BsmI, TaqI, ApaI and FokI of vitamin D receptor and vitamin D influence on goiter development.
Methods
One hundred and fifty two women-96 with and 56 without nontoxic goiter were examined in 2014. In US examination we calculated the volume of the thyroid gland and volume of nodules. Blood samples for 25-(OH) D total and genetic research were taken. We made statistical analysis of correlation between volume of the thyroid gland, volume of the nodules and levels of vitamin D in groups of various polymorphisms.
Results
Ninety-six women with goiter size from 5.67 to 68.85 ml– mean 19.7 ml, median 15.6 ml, the total nodules volume varied from 0.1 to 39 ml mean 4.59 ml, median 0.94 ml and the control group of 50 women with thyroid volume in normal range from 5.1 to 19.9 mean 11.2, median 11.2 ml. The 25(OH)total levels varied in control group from 5.3 to 31.8 ng/ml, mean – 14.4, median 12.95, and in goiter group from 4.7 to 39.8 ng/ml, mean 15.00, median 13.3 ng/ml. Only 14% in control and 22% in goiter group had vitamin level over 20 ng/ml. We found no correlation between vitamin D level and volume of thyroid gland in goiter group and no correlation between vitamin D level and summary volume of the thyroid nodules. We analyzed all alleles variants of VDR polymorphisms in groups with and without goiter in correlation with vitamin D level. We did not found statistical correlation between VDR polymorphisms BsmI, TaqI, ApaI and FokI using x^2 test with goiter size or nodules size.
Discussion
VDR polymorphism may have role on impact of vitamin D deficiency on osteoporosis, osteomalacia development but we did not find change of action of vitamin D on goiter development in any type of studied polymorphism - BsmI, TaqI, ApaI and FokI. Common Vitamin D deficiency in polish population have no significant influence on goiter development independent from VDR BsmI, TaqI, ApaI and FokI polymorphism

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EP171

An unusual presentation of Graves' Ophtalmopathy: About 3 cases

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Introduction
Dysthyroid ophthalmopathy corresponds to eye damage encountered in various thyroid diseases. It is seen mainly in Graves' disease, and may develop any time in the course of the disease evolution. Clinical presentations of Gravesâ€™

ophtalmopathy (GO) are extremely heterogeneous. GO may be sight threatening in 3–5% of cases, and then represent an emergency requiring immediate treatment. We report three cases illustrating a particularÂ Â Â presentation of these orbitopathies.
Observation 1
A 61 years old man, followed for 1 year for Graves' disease (GD) with Carbimazole 10 mg / day, presents for 4 months bilateral exophtalmopathy with lid retraction predominant at the left eye, associated with retroorbital pain. Clinical examination found a homogeneous goiter grade 1. Visual acuity was to hand movements on the right and light perception on the left. He had an important chemosis, Mourits score at 7/10 for left and 5/10 right. The patient had corneal abscess having evolved under intravenous antibiotics. For orbitopathy, our patient received three consecutive boluses of methylprednisolone 1 gÂ daily , then 6 weekly bolus of 500 mgÂ Â then 250 mgÂ Â for 6 more weeks with a good evolution.
Observation 2
A 41 years old man, who had a total thyroidectomy 1 month ago for GD, with hormonal replacement. He presents since 5 months an exophthalmopathy with inocclusion of the left eye. He had an opaque cornea with significant chemosis, quoted 7/10 according to Mourits score. Patient wasÂ receivedÂ intravenous corticosteroids: 3 daily bolus of methylprednisoloneÂ 1 g / day, then 500 mg / week for 6 weeks and 250 mg /week for 6 weeks. The outcome was favorable, with persistent corneal opacity.
Observation 3
A 70 years old woman, followed for 3 years for multinodular goiter which progress like GD. She was treated by Carbimazole. She presented for 1 month a bilateral exophthalmopathy with eyelid and conjunctival edema. She had a grade 2 goiter with two nodules, respectively measuring 1 to 2 cm. Visual acuity was reduced with chemosis and conjunctival hyperemia. Our patient received 12 bolus ofÂ injectable steroids: 500 mg /week for 6 weeksÂ Â then 250 mg/ week with good evolution.
Conclusion
GO is a complex inflammatory disorder that is better managed by a multi-disciplinary team.Â Â An appropriate assessment of both severity and activity of the disease warrants an adequate treatment. Intravenous glucocorticoids remain the treatment of choice for active moderate to severe disease.

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EP172

BRCA1 mutations and polyporphisms in women with and without goiter

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Objective
There are many suggestions of predispositions to goiter in women with benign and malignant masthopaty, we looked for BRCA1 mutations in women wit and without goiter
Methods
One hundred and fifty two women-96 with and 56 without nontoxic goiter were examined in 2014. In US examination we calculated the volume of the thyroid gland and volume of nodules. Blood samples for BRCA1 were taken, ex05 - p.Cys61Gly; ex 11 polymorphisms K1183R, mutations: c.3819del5, c.3875del4, c.3986delT, c.4154delA; ex20 mutations: 5382insC, 5370C>T
Results
Ninety-six women with goiter size from 5.67 to 68.85 ml– mean 19.7 ml, median 15.6 ml, the total nodules volume varied from 0.1 to 39 ml mean 4.59 ml, median 0.94 ml and the control group of 50 women with thyroid volume in normal range from 5.1 to 19.9 mean 11.2, median 11.2 ml. The 25(OH)total levels varied in control group from 5.3 to 31.8 ng/ml, mean – 14.4, median 12.95, and in goiter group from 4.7 to 39.8 ng/ml, mean 15.00, median 13.3 ng/ml. Only 14% in control and 22% in goiter group had vitamin level over 20 ng/ml. We found no one pathogenic mutation in any group, and polymophisms on ex 11 were represented in similar number in goiter and non goiter group.
Discussion
Goiter is very common condition in polish female population over 40, rare BRCA1 mutation were not found in the research group and common polymorphisms do nod differ groups with and without goiter.
Conclusion
We need probably bigger group do make final conclusion, but on the basis if our research there is no increased incidence of BRCA1 mutations and polymorphism in goiter women.

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EP173

Simultaneous occurrence of papillary and medullar thyroid carcinoma report of a case

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Introduction
Mixed thyroid carcinoma is an entity that corresponds to tumors with a double component: one of the vesicular type (Tg +) and the other of the medullary type (CT +). We report the occurrence of papillary and medullary thyroid carcinoma in a 44-year-old patient. This coexistence is considered rare.
Case
A 44-year-old patient underwent a thyroidectomy due to a goiter, histopathological examination identified multifocal papillary carcinoma, multiple colloidal nodules, with metastases in supra isthmic and left supraclavicular lymph nodes. A complement by iratherapy was performed, with bilateral cervical lymph node dissection, which revealed: bilateral *jugular* chain metastases, three metastases in the recurrent chain with capsule invasion. The *mediastinal lymph node dissection showed* seven metastases with capsule invasion, immunohistochemistry confirmed the presence of calcitonin. For the extension assessment: Postoperative calcitonin = 228 ng / l. CT scan revealed: *empty thyroid* bed, bilateral submandibular nodes, intraparenchymal and subpleural lung nodules, *bilateral axillary lymphadenopathy*, *Hepatic steatosis* and an osteocondensation lesion at the inferior angle of the left scapula. Bone scintigraphy: no sign of secondary bone localization.
Discussion
The Simultaneous occurrence of medullary carcinoma with a differentiated carcinoma of the thyroid, although exceptional, should always be considered as it could change the therapeutic approach and the prognostic evaluation.

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EP174

Graves' ophthalmopathy presenting with hypothyroidism

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Introduction
Graves' disease is a multi-system autoimmune disease characterized by hyperthyroidism, ophthalmopathy and pretibial myxedema. The disease presents with hyperthyroidism or more rarely with ophthalmopathy. It runs a various course and many times during its natural course permanent hypothyroidism may ensue.
Aim
The aim was to describe the case of a patient with Graves' disease presenting with ophthalmopathy and subclinical hypothyroidism.
Case description
A patient, female, aged 59 years, presented with proptosis of the right eye and other symptoms such as a sense of foreign body within the eyes. A CT scan of the orbits was performed which showed increased volume of the extraocular muscles of both eyes, which was prominent in the right eye. A laboratory evaluation showed TSH receptor antibodies marginally positive 1.7 IU/l (normal values <1.5 IU/l), positive microsomal and antithyroglobulin antibodies, TSH 4.9 mIU/l and FT_4 normal. Methylprednisolone was administered 500 mg/wk iv for a period of 6 weeks followed by tapering of prednisolone orally. The proptosis of the right eye improved. A new laboratory evaluation showed TSH 5.7 mIU/l. Thyroxine was administered at a dose of 75 μg daily. The patient is stable and euthyroid, TSH being 2.1 mIU/l on thyroxine and low dose prednisolone.
Conclusions
The case of a patient with Graves' disease is described which presented with ophthalmopathy and subclinical hypothyroidism. In Graves' disease permanent hypothyroidism may develop over the course of the disease. However, presentation of the disease with subclinical hypothyroidism is very rare and underlines the relationship, as far as pathogenesis and pathophysiology is concerned, between autoimmune Hashimoto thyroiditis which causes hypothyroidism and Graves' disease, a multi-system autoimmune disease characterized by multiple organ system involvement and hyperthyroidism.

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EP175

Cretinism and language delay are rare manifestations of central hypothyroidism: 2 cases report

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Cretinism and neurological impairment are related to primary hypothyroidism (PHT) while children with central hypothyroidism (CHT) are usually diagnosed during the investigation process for short stature.
Objective
To describe two children with unusual presentation of CHT.
Case 1
Baby girl, born after 38 weeks of gestation, weighing 3000 g, and measuring 49.5 cm long was admitted when 3 months old. The parents reported stunted neurological development and difficulty in gaining weight. Neonatal screening: TSH < 0.1 mU/ml. A typical cretinism face was observed, with depressed nasal base, pig nose and infiltrated eyelids associated with umbilical hernia, reduced muscle tone, short length (< P10) and low weight (< P10). Biochemical analysis: Free T_4 < 0.1 ng/ml, Total T_4 = 0.9 ng/ml, TSH < 0.1 mU/ml and IGF-I: undetectable. Following thyroxin replacement, there was an improvement in the neurological development, height velocity and weight gain. IGF-I concentration increased to 70 ng/ml(P50). At the age 4.5 years, she was readmitted to the clinic after the treatment had been discontinued for 1.5 year. Her features were typical of severe cretinism with slow movements, difficulty in walking and height velocity close to 0 cm/yr and serum IGF-I level: undetectable. A low thyroxin treatment (1.5 ug/Kg per day) was initiated with full recovery of the cretinism features and neurological impairment.
Case 2
Baby girl, born after 38 weeks of twin pregnancy, weighing 2680 g and measuring 47 cm long. Neonatal screening: TSH = 0.4 mIU/ml. She was admitted to the clinic when 1.7 years referring language delay. Initial investigation: TSH = 1.3 mIU/ml and total T_4 = 5.4 mg/dl. Significant improvement in language development occurred after thyroxin replacement. Serum TSH and total T_4 during treatment were 0.6 mIU/ml and 7.6 mg/dl and change to 1.5 mUI/ml and 5.7 mg/dl, respectively thyroxin was discontinued for investigation purposes. Molecular analysis of the deceased twin brother revealed c.826G > A p.G276R mutation of *MCT8* in the X chromosome (Xq13.2), in heterozygosis. *MCT8* encodes the monocarboxylate transporter-8 (MCT8), responsible for the transmembrane transport of T_3 into the neuron.
Conclusion
Although rare, neurological and developmental related symptoms can be the leading finding to the diagnosis of CHT. Depending on its aetiology, CHT can be associated with cretinism and extremely low TSH and thyroxin levels. Thyroxin determination should be considered in cases of undetectable/extremely low TSH in order to prevent adverse outcomes. Regarding the *MCT8* mutation, the severity of clinical findings is variable and changes in neurodevelopment and mental retardation are more frequently observed in male patients.

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EP176

Strumectomy in nodular goiter - does it make sense? Reflections after 22 years of observation of one patient

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Introduction
Although the thyroidectomy is one of the most frequently performed operations in endocrine surgery, indications for this procedure as well as recommendations for further observation are still controversial. Therefore we would like to present what is happen with our patient during 22 years after thyroid surgery.
Case report
In 1995, at the 46-year-old woman at that time, a subtotal strumectomy was performed due to the nodular goiter. Postoperative histopathological examination revealed *struma colloides macro et microfollicularis* and *adenoma folliculare.* During the next 12 years, a thin-needle aspiration biopsy aimed at focal lesions with mixed echogenicity of the thyroid gland was performed 4 times. The last one in January 2012, without malignant features. But in 2010, the Sjoegren syndrome was diagnosed, treated with prednisone and methotrexate, and nodular changes in both lungs. 2012 she suffer under heart attack. 2014 in view of the enlargement of nodules in the lungs, upper right lobectomy was performed. The histopatological result: metastases from well-differentiated thyroid cancer, maybe follicular TTF-1 (+) TGB (+). Unfortunately preparations from 1994 were no longer available. The total strumectomy was performed but in the histopathological examination only sings of struma nodosa colloides were found. Further treatment with J131 was complicated by anemia, leukopania and thrombocytopenia.
Discussion
We do not know where thyroid cancer cells came from in the lungs. Probably from an outbreak existing in the removed thyroid, and not detected during the post-operative examination. If so, we do not know why the symptoms appeared only after 11 years, or whether the treatment of Sjoegren's syndrome accelerated the growth of cancer.
Conclusion
The lack of malignant traits in the histopathological material originating from the strumectomy does not give confidence and it certainly does not give a guarantee of successful long-term results.

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EP177

Simultaneous medullary and papillary thyroid cancer in Graves-Basedow disease. Two case reports

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Introduction
The occurence of simultaneous medullary and papillary thyroid cancer is very rare. There were only 17 case reports in the literature, and fewer with Graves-Basedow disease associated. A retrospective study conducted at the National Institute of Endocrinology 'C. I. Parhon' showed that 7,6%of the patients who underwent total thyroidectomy for Graves-Basedow disease had thyroid cancer. Recent studies show that specific cellular pathways are determined by the binding of anti-TSH receptor antibodies stimulating cellular growth and invasion and angiogenesis.
Case reports
We present two cases diagnosed with Graves-Basedow disease with total thyroidectomy and a histopathological report that showed the simultaneous presence of a papillary and medullary thyroid cancer.
Conclusions
Graves-Basedow disease can be associated with differentiated thyroid cancer and medullary cancer in the same patient.

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EP178

A rare case of hurthle cell adenoma and parathyroid adenoma

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Introduction
Hurthle cell of adenoma (HCA)of thyroid gland is rare neoplasms of the thyroid. They have been found in association with various benign thyroid conditions like Hashimoto's thyroiditis, hyperthyroidism, nodular goiter, and thyroid neoplasms; where they often represent oncocytic metaplasia. Oncocytic cells are also present in normal parathyroid tissue. Oncocytic parathyroid adenomas, predominantly (more than 70%) or exclusively composed of oncocytic cells are rare (4.4 to 8.4%). We report a patient with an extremely unusual clinical presentation of Hürthle cell adenoma in thyroid and parathyroid adenoma.
Case presentation
We presented a case that of a 50-year-old woman with neck swelling. There were no associated pain or pressure symptoms. Ultrasonography showed a nodule 2 cm diameter in left and showed a nodule 2.5 cm in right thyroid lobewith central and peripheral blood supply. Fine-needle aspiration revealed cellular smears containing monotonous oncocytic cells arranged in monolayered sheets and pseudopapillary structures. No abnormality was detected on the laboratory. Thyroidectomy was done and microscopic examination revealed a HCA of the left thyroidnodule and oncocytic parathyroid adenoma in right thyroid lobe. The patient was discharged on thyroid replacement therapy and has remained healthy after more than 36 months of follow-up.

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EP179

Prognostic factors affecting neck lymphnode recurrence and distant metastasis in papillary thyroid cancer: results of a study in 40 patients

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Objectives
Overall, papillary and follicular carcinoma is associated with a 30-year cancer-related death rate of 6 and 15%, respectively. Poorer outcomes have been associated with older age, male gender, tumor size, grade and extrathyroidal extension. We investigated the clinical and laboratory characteristics of 40 patients who presented recurrence of thyroid disease.
Patients data
- 40 Patients (21 Females and 19 males) with papillary thyroid cancer and recurrence of the disease.
- Mean age ± s.d. of last follow-up: 54.68 ± 16.24 years.
- Mean age ± s.d. of surgery 47.57 ± 15.57 years.
- Mean years ± s.d. after surgery of lymph nodes meta: 1.55 ± 2.52 years.
- All with papillary thyroid carcinoma, 15 (62.5%) with aggressive type and 25 (37.5%) with no aggressive type.

Results
TG and ANTI-TG measurement in different time points (Mean value ± s.d.):
- TG in first postoperative control with stimulation: 20.54 ± 26.65 ng/ml and 20% of patients had positive anti-TG.
- TG measure at diagnosis of lymph nodes metastasis: 52.95 ± 137.40 ng/ml and 17.5% of patients had positive anti-TG.
- TG measured at last follow-up control: under suppression therapy: 3.59 ± 12.20 ng/ml. And Tg under stimulation: 6.57 ± 14.36 ng/ml. 17.5% of patients had positive anti-TG in the last follow-up control.

Total I-131 Dosis: 252.75 ± 169.44 mCi. At the first post-therapy WBS all the patients had uptake only in the neck, whereas at the last WBS (post-therapy or diagnostic) 11 patients (27.5%) had negative uptake. When examining the lymph nodes with U/S, nine patients (22.5%) had reduction of the maximal diameter, 23 patients (57.5%) had no change in the maximal diameter and eight patients (20%) had an increase in the maximal diameter of the suspicious lymph node. Two patients (5%) presented with a distant metastasis. Over the time of follow-up, six patients (15%) increased, and 26 patients (65%) reduced the TG levels. Furthermore, over the time of follow-up three patients (7.5%) increased, and three patients (15%) decreased the anti-TG levels.
Conclusions
The recurrence of the disease can be presented clinically with symptoms like dysphagia, dyspnea, voice changement or with a palpable mass in the neck. The biochemical recurrence concerns the increase in Tg of anti-Tg levels and the anatomical recurrence refers to disease detected in Ultrasound, Whole Body Scan, CT, MRI or PET/CT. With all these tests the recurrence can be detected before it is clinically evident.

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EP180

The association of breast cancer and thyroid cancer: what relationship? (Preliminary results)

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Background
Several studies have demonstrated the relationship between breast cancer and thyroid cancer by the presence of common genetic determinants as well as hormonal factors. The aim of the study was to define the prevalence of breast cancer among patients followed for thyroid carcinoma and to determine the factors that favor this association.
Materials and methods
A Cross-sectional study was conducted in Endocrinology and Diabetology department of IBN Rochd University Hospital of Casablanca, including 50 patients followed for thyroid carcinoma between 1986 and 2017 among all the differentiated carcinomas of the thyroid (614 patients) and presenting breast cancer. Statistical analysis performed by the software SPSS.16
Results
Prevalence of patients presenting breast cancer and thyroid cancer was 8.1% with female predominance. The mean age was 56 (35–72) years. Family history of neoplasia was found in 60% of cases. Breast cancer preceded the discovery of thyroid cancer in half of the cases with a delay of 5.8 years (6 months and 20 years). Iratherapy was performed in all patients. External radiotherapy was realized in 47% of cases for the treatment of breast cancer. Papillary carcinoma was the predominant histological type (93%). Predictor factors of this association were female patients who had the first neoplasia at a young age (<45 years), family history of neoplasia and prior external radiotherapy.
Conclusion
While waiting for confirmation of these preliminary results, several authors recommend greater vigilance regarding early detection of thyroid cancer in patients treated for breast cancer.

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EP181

Association thyroid carcinoma and lung adenocarcinoma

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Introduction
Pulmonary adenocarcinoma is an epithelial tumor with differentiation glandular whose frequency increases sharply. The association with cancer thyroid is rare. In this context, we report a medical observation.
Observation
A 58-year-old patient with no history of smoking was admitted to one of our departments. Thyroidectomy 4 years ago, the pathological study a poorly differentiated carcinoma of 4.5 cm, class PT2 TNM. Our patient had benefited from an iodine 131 therapy course with a complete CT scan of body showing a white isotopic map. Thyroid suppressing the dose with bad adherence. She experienced exercise dyspnea and pain thoracic for 3 years, aggravated by a respiratory distress. A scanner showed a left lower lobe of 28 mm and a mass nodular of the same lobe of 20! 32 mm.
Objective bronchoscopy bronchitis chronic without suspicious cells identifiable on the biopsy. A lobectomy left was found, which revealed a primary pulmonary glandular (positivity TTF1 and CK7).
Conclusion
This observation shows the coexistence of multiple malignancies in a patient, whose diagnosis and treatment may be delayed, which aggravates the prognosis.

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EP182

The concept of idiopathic myxedema: The relationships between hypothyroidism and ATPO evolutive level

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Background
Hashimoto thyroiditis (HT) is defined as thyroid chronic inflammation due to high level antithyroperoxydase antoantibodies (ATPO) and/or antithyroglobuline autoantibodies (ATG) and their destructive process on thyroid cell. The diagnostic uses specific and very characteristic ultrasound features. What diagnosis has to have those patients with ultrasound features of HT, who are hypothyroid, but with normal levels of ATPOs *and* normal levels of ATGs ?
Method
i) ATPO and ATG levels were analyzed in accreditated Bucharest laboratories. ii) We considered HT those patients with high ATPO/ATG levels, cut off over 34 ui/ml. iii) FT_4 and TSH were considered for functional diagnostic. iv) Thyroid ultrasound was done with a 7.5–10 MHz probe. v) Idiopathic means: I do not know what it is, after eliminating all I know !
Results
A. Patients: 3962. **B.** Based on ATPO/ATG level we considered: i) HT: 1753; ii) thyroiditis with only high ATG (ATPO normal): 205; iii) Other thyroid diseases

(mostly nodules): 1878 - ATPO/ATG normal, 1729 euthyroid, 113 hyperthyroid, no TRAB, 38 identified cause of induced hypothyroidism. iv) *Special patients with hypothyroidism with normal ATPO and normal ATG, without any intervention on thyroid (thyroidectomy, 131-I) or neck area (radiation for lymphomas) and ultrasound features indicating inflammation*: 205.
Discussion
ATPO evolution in HT is mostly undulatorious (Ratcu, this congress). In some patient, ATPO decreased under the cut off limit, if they had no thyroid, through thyroid interventions, and thyroid atrophy. These patients were hypothyroid. It is possible in evolution when the antigen (thyroid) disappeared, the autoantibodies disappeared, too ! Like in special patients described in point 4 ?
Conclusions
1. Those patients who are hypothyroid, without a known and identifiable causes of hypothyroidism, who present obvious ultrasound sign of HT, but in who ATPO and ATG is in normal limits, have to be considered as idiopathic myxedema.

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EP183

The frequency, specification of diseases of thyroid gland at children and teenagers according to data for 5 years and the kinds of surgical treatment"

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The aim
To study the frequency, specification of diseases of thyroid gland at children and teenagers according to data for 5 years and the kinds of surgical treatment
Material and methods of investigation
Under supervision of the employees of the department of children's endocrinology the Center of Endocrinology of PH of RUz during from 2012 to 2016 years was hospitalized 213 children and teenagers with various diseases of thyroid gland, from them of the boys was - 67 (31.4%), girls -146 (68.5%). 20 sound children and the teenagers of the appropriate age made the group of the control.
Results
The most of patients were in teenager age, namely from 11 to 17 years - 147 patients (69.1%), were at the same time mostly sick girl - 100 from 147 (68.0%). Greater part of patients on turned was made by patients with congenital hypothyroidism- are 94 cases (44.1%), on the second place - the mixed goiter is 35 supervisions (16.4%), on the third - a diffusely-toxic goiter is 30 patients (14.0%), and also diffuse goiter of 1-2 degree - 19 (8.9%), autoimmune thyroiditis - 14 (6.5%), multinodular goiter - 15 (7.0%), sharp festering strumitis - 2 (0.9%), papilliferous adenocarcinoma - 2 (1.0%). To the patients the different spectrum of surgical help was executed, a total thyroidectomy - 14 (34%) supervisions, hemistrumectomy was most often executed here - 10 (24%) cases, large resection of lobuli - 6 (14.5%), etc.
Conclusions
The results received by us confirm need of further long observation and treatment of patients.

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EP184

Role of thyroid dysfunction in patients with menstrual disorders

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Menstrual disorders pose a huge burden on gynecology OPD, accounting for approximately 20% of attendance Thyroid hormones play an important role in reproductive function by direct effects on ovaries and indirectly influencing on sex hormone-binding globulin. Thyroid impairment can cause menstrual irregularities and infertility. In India, thyroid disorders are most common endocrine diseases. Thyroid disorders manifestation increases with age, and approximately 26% of premenopausal and menopausal women have thyroid pathology. Thyroid disorders are more common in women than in men and older people suffer more often than younger age groups. Hypothyroidism is linked to a large range of reproductive disorders: abnormal sexual development, menstrual irregularities, and infertility. The impact of hypothyroidism on the menstrual cycle has been identified since the 1950s and it leads to changes in cycle length and blood flow. Subclinical hypothyroidism has been associated with occult menorrhagia (mild disturbances in menstrual volume and duration) before becoming symptomatic. Subclinical hypothyroidism occurs in 9.5% of women. Hyperthyroidism manifesting before puberty delays the menarche. In women of fertile age, oligomenorrhea and amenorrhea are the commonest abnormalities associated with hyperthyroidism. These irregularities sometimes precede thyroid dysfunction. Nowadays subclinical hyper- and hypothyroidism can be diagnosed very early, while a few decades ago they would have passed undiagnosed. Timely detection of thyroid pathology in patients with menstrual disorders and management can prevent surgeries like curettage and hysterectomy. Thyroid autoimmunity is reported to be associated with various kinds of thyroid dysfunction. Number of foreign studies show association of thyroid dysfunction and menstrual disorders, but there are not many Indian studies in this regard.
Conclusions
There is a strong correlation between thyroid dysfunction and menstrual disorders. Timely diagnosis and treatment of thyroid pathology in patients with menstrual dysfunction leads to settlement of the menstrual irregularities, and avoidance of unnecessary interventions such as hormonal therapy and surgery. Menorrhagia followed by hypo/oligomenorrhea and polymenorrhea are the most commonly observed menstrual abnormalities. Since thyroid dysfunction is an important treatable cause of menstrual disorder, thyroid status examination should be done in patients with menstrual disorders. Prevalence of subclinical hypothyroidism in patients with menstrual dysfunctions emphasizes the need to detecting the hypothyroidism at this stage, so that treatment can be initiated on time. Anti-TPO antibody test is an expensive routine test recommended to patients with menstrual disorders. However, prospective studies are required to analyze the cost effectiveness of anti-TPO antibody testing and its possible benefits to treatment.

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EP185

It is a link between gallstone disease and pathology of thyroid gland

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Introduction
Gallstone disease is one of most common in the Europe with prevalence till 15%. The basic mechanism of stone formation is precipitation of cholesterol crystals in the supersaturated bile. The relationship between thyroid function and the content of cholesterol has been known for quite a long time, as well as the work confirming the relationship between hypothyroidism and cholelithiasis. Recently, in mice it has been shown that both hypothyroidism and hyperthyroidism promote the formation of gallstones, although in other mechanisms. Cholecystectomy, despite the changing range of indications for its implementation remains an important method of treatment of the consequences of cholelithiasis. That is why we would like to present our observation in which the starting point was cholecystectomy.
Aim
The aim of our study was the prospective observation of patient after cholecystectomy where the place of observation was an endocrinology out-patients clinic
Results
In years 2002–2008 in our hospital 1125 cholecystectomy was performed (1025 laparoscopic). In the same years, 127 (11%) of these patients were treated our endocrine outpatients clinics due to thyroid diseases. Among the patients treated for thyroid diseases, the most numerous were diagnosed as nontoxic goiter (E04 = 49%), followed by hyperthyroidism (E05 = 19%) and hypothyroidism (E03 = 17%)
Conclusion
Of course, our observation from one hospital has many limitations. It cannot be ruled out that the effect on the frequency of visits to the outpatients clinic had already existing contact with the health service and / or the requirements for the assessment of the thyroid status before the procedure set by surgeons.However, a fairly high incidence of thyroid problems in patients undergoing cholecystectomies prior to surgery and in the following years would speak for a link between thyroid diseases and cholelithiasis.

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EP186

Graves' disease in a patient with myasthenia gravis: a case report

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Introduction
Myasthenia gravis is an autoimmune neuromuscular disease characterized by the presence of anti-acetylcholine receptor antibodies. It can be isolated or associated with other auto-immune conditions. Graves' disease is an autoimmune disorder typically characterized by the presence of circulating autoantibodies that tie to and stimulate the thyroid hormone receptor. Coexisting myasthenia gravis and Graves' disease is a rare but well recognized condition. The physiopathology of this association has not been clearly established. We report the case of a woman with known generalized myasthenia gravis who developed Graves' disease 15 years after.
Observation
A 43-year-old woman was referred to our department for thyrotoxicosis. Her past medical history was remarkable for generalized myasthenia gravis. In fact, at the age of 28 years, the patient presented with a fluctuating muscle weakness, difficulty swallowing, double vision and fluctuating ptosis. The diagnosis of myasthenia gravis was established. Then, the patient had a total thymectomy and treated with pyridostigmine. On physical examination, she had homogenous goiter and bilateral exophthalmos. Thyroid laboratory investigation revealed overt hyperthyroidism. The diagnosis of Graves' disease was established and the patient was initially treated with antithyroid drugs. Then, she was referred to the department of Nuclear Medicine for a radioactive iodine therapy.
Conclusion
The occurrence of Graves' disease and myasthenia gravis in the same patient indicates a genetic predisposition to autoimmune diseases. Muscle weakness may be the first symptom of thyrotoxicosis as well as myasthenia gravis, so a distinction between the two autoimmune diseases can be difficult in some situations. The myasthenic syndrome may precede hyperthyroidism as was the case of our patient or may appear sometimes during the treatment of hyperthyroidism. Propranolol treatment is contraindicated and radical treatment of hyperthyroidism is required.

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EP187

Case report and literature review. surgical management of hyperthyroidism in pregnancy

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Hyperthyroidism during pregnancy is determined by decreased thyroid stimulating hormone (TSH), and high levels of thyroid hormones: thyroxine (T_4), triiodothyronine (T_3), being a complication in 1–2 women per 1,000 pregnancies, and occurs first as Graves' disease in 0.1–1% of pregnancies. There are specific reference ranges of THS and free T_4 for each population and each trimester. For the medical management in the first trimester it is recommended propylthiouracil, and for second and third trimester is methimazole. The surgical management is recommended in the second trimester in cases of intolerance to the medication, such as allergies or agranulocytosis. Next, we describe three cases of pregnant patients who undergo surgical management with total thyroidectomy, because of intolerance to medication during second trimester, previous management with lugol. The three patients received levothyroxine post-surgical. Literature review is made.
Case 1
Age 28, gestational age = 16.2 weeks. Diagnosis before pregnancy. TSH = 0.00 uiu/ml, free T_4 = 7.77 ng/dl. At physical examination with tachycardia, hypertension, trembling limbs and aortic heart murmur. Thyroid US with heterogeneous echogenicity, echocardiogram with mild pulmonary hypertension. Initial medical treatment with methimazole 30 mg/day, lugol 6 drops every 8 hours for 10 days. Total thyroidectomy carried out without any complications. TSH = 0.007, free T_4 = 2.95 ng/dl (post-surgical). Pregnancy termination; weight 3.100 grams and size 48 cm.
Case 2
Age 26 years, gestational age = 16.3 weeks. Diagnosis before pregnancy. TSH = 0.005 uiu/ml, free T_4 = 5,7 ng/dl. At physical examination with tachycardia, hypertension, trembling limbs. Thyroid US with diffuse goiter. Initial medical treatment with Methimazole 40 mg/day, lugol 6 drops every 8 hours for 10 days and corticosteroids. Total thyroidectomy carried out without any complications. TSH = 2,4 uiu/ml, free T_4 = 1.23 ng/dl (post-surgical). Pregnancy termination at 38.5 gestational weeks; weight 2.946 grams and size 48 cm. TSH = 3.1 uiu/ml and free T_4 = 1.09 after pregnancy.
Case 3
Age 21 years, gestational age = 17 weeks. Diagnosis before pregnancy. TSH = 0.003 uiu/ml, free T_4 = 6.5 ng/dl. At physical examination with tachycardia, hypertension, trembling limbs and auricular fibrillation. Thyroid ultrasonography with multinodular goiter Trads 3. Medical treatment before surgery with Methimazole 50 mg/day with intolerance, lugol 6 drops every 8 hours for 10 days and corticosteroids. Total thyroidectomy carried out without any complications. TSH = 2.7 uiu/ml, free T_4 = 0.98 ng/dl (post-surgical). Pregnancy termination at 39.1 gestational weeks; weight 3.129 grams and size 49 cm. TSH = 1.76 uiu/ml and free T_4 = 1.2 after pregnancy.

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EP188

Comparison of results of cytological and hystological research of thyroid gland nodes

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Purpose
To assess the sensitivity and specificity of the cytomorphological method in the diagnosis of the nosological variant of nodal goiter.
Materials and methods
A comparison of the results of cytological and histological studies of thyroid nodules in 36 patients (15 women and 11 men, average age 54.2 ± 9 years), operated for nodular goiter. Cytological findings were divided into 4 categories: 'non-informative material', 'benign lesion', 'follicular neoplasia', 'malignant formation'.
Results
The analysis of the results of cytological research showed that 17 (47.2%) cases were given the conclusions 'non-informative material', 14 (38.9%) 'benign lesion', in 5 (13.9%) - 'follicular neoplasia', and not a single conclusion 'malignant formation'. According to the results of histological examination, in 10 (58.8%) cases, colloidal proliferating nodes were diagnosed in different categories, in 6 (35.3%) - follicular adenoma, in 1 (5.9%) - papillary cancer. Among the conclusions of the category 'benign lesion' in 9 (64.3%) cases, according to the results of histological examination, colloidal proliferative nodes in different degrees were diagnosed, in 5 (35.7%) - follicular adenoma. Among the conclusions of the category 'follicular neoplasia' in 3 (60%) cases - follicular adenoma, in 1 (20%) - colloidal proliferative nodes in different degrees, in 1 (20%) - papillary cancer. The sensitivity of the cytomorphological method of diagnosis of 'nodular colloid goiter' was 44%, specificity-69%, 'follicular neoplasia' 20 and 91%.
Conclusions
The results of the study showed a high percentage of the conclusions of the category 'non-informative material' and identified malignant formations in this category, which significantly reduces the sensitivity of the cytomorphological diagnostic method at the preoperative stage with nodular goiter and requires unification and optimization of both FNA and cytological classification.

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EP189

Incidence of thyroid cancer among patients with thyroid nodules

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Introduction
Thyroid nodules are observed in 8% of the entire population and have a 5–15% prevalence of malignancy. Thyroid cancer is the most common endocrine neoplasia. Advancements in diagnostic tools such as fine needle aspiration (FNA) are linked to an increasing incidence of thyroid cancer worldwide. The objective of this audit was to evaluate thyroid nodules and to determine the incidence of malignant and benign tumours.

Methods
This retrospective cohort study collected data from eight patients who presented with thyroid nodules. Ultrasound/FNA results of thyroid nodules were used to measure the incidence of thyroid cancer.
Results
The number of thyroid nodules diagnosed as malignant was significantly greater than benign nodules (P-value <0.0001, 95% confidence interval (-1.168 to -0.5459)). This data indicates that females are more likely to develop thyroid cancer than males.
Conclusion
The incidence of thyroid cancer is growing at a rapid pace. This is largely due to the development of radiological tools. In particular, the utilisation of these tools in diagnosing small impalpable thyroid nodules. Papillary carcinoma is the most common thyroid cancer associated, as well as having the highest mortality rates. Notably, it is also the most likely diagnoses in impalpable sub-centimetre thyroid nodules. Analysis of gender data shows females are more likely to develop thyroid cancer than males.

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EP190

Insights from large-scale mHealth data: the impact of Levothyroxine dosage on intensities of symptoms experienced by Hashimoto's patients

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Hashimoto's thyroiditis is the most common autoimmune condition, with increasing number of people being diagnosed and experiencing varying ranges of symptomes and intensities. This makes the diagnosis as well as treatment challenging. The benefit of preventive health management strategies has been successfully working for diabetes type 2, where condition is managed through implementation of healthy lifestyle and patient-doctor shared decision making. Health care today is increasingly digital, with millions of patients using health apps to track their symptoms and report to doctor. Health apps can serve as research tools to understand behavioural patterns influencing health outcomes. We have investigated a correlation between the medication type, dosage and adherence to commonly experienced symptoms such as fatigue, focus and weight in different cohorts of people diagnosed with Hashimoto's. We observed that the increasing doses of levothyroxine do not scale in relieving symptoms experienced by Hashimoto's patients. Further management might be necessary to relieve from the most common symptoms, such as focus, muscle pain and digestion issues. This is specifically true for patients experiencing digestive problems, which seem to be independent of medication, but can impact and intensify other thyroid-related symptoms. Next, we have investigated whether using medication reminders (alarms) and making peer-reviewed information available to patients via the mHealth app will result in symptom improvement as well as normalizing BMI and will report our findings in detail at the meeting.

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EP191

Autoimmune thyroid disease (Hashimoto thyroiditis) disscussions as possible predicting of thyroid papillary microcarcinoma (MPTC)

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It's have been reported, that an evidence a mixture of immune cells frequently found inside, or surrounding primary thyroid microcarcinoma. In this point of view, we support the concept, that the immune system, such autoimmune thyroid disease, may interfere or predict in thyroid carcinoma or microcarcinoma development and progression. Arising in nonneoplastic tissues, local immune response under autoimmune chronic thyroiditis would be associated with Hashimoto parenchyme atypia converts in classical papillary carcinoma or its precursors (gray zone lesions). Most of this tumors are diagnosed incidentally. Based of the our data, we conclude, that Hashimoto thyroiditis have some distinct histo- and immunopathological features involving in thyrocytes and extra-follicular domens differences. Our data ($n=155$), collecting and clasifical according to TBSRTC, were shown, that in Hashimoto parenchyme comprised most of immature follicular cells (solid nest cells) estimating as thyroid stem/progenitor cells with some atypia, high mitotic and invasive potentialities. Results obtained by Cyclin-depending Kinase activities detection, indicate on the high prevance of Cyclin D1/E and Galectin-3 expression in Hashimoto thyroiditis and support the current concept about the asossiation of 'carcinoma - type' immature follicular cells with gene amplification in micro papillary thyroid carcinoma and autoimmune thyroiditis.

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