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Prize Lectures and Biographical Notes
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.
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).
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.
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 is 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 furthred 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.
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 Estrelot 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 DMA1, dimethyl androstanol 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 hypothenums, parietal 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 iodindaminide derivatives, cause premature spermatogenesis and infertility. Eppin (epidymyideal protease inhibitor) secreted by Sertoli cells is also a potential target. Anti-Eppin antibodies inhibit human spermatozoa motility. Blocking CatSper (caticionic 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 available methods 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 contraception, 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
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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 as 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. Reactivation 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 re-fed 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.

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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 gonad 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 might 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. A number of T2D animal models have been developed to study the relationship between T2D and cognitive impairment. Among them, the STZ induced diabetic rat model has been widely used to study T2D cognitive impairment. However, recent studies indicate that the manifestation of cognitive impairment in STZ diabetic rats is based on the presence of moderate to severe retinopathy, which limits the potential of this model for the study of the mechanisms underlying the T2D cognitive impairment. To overcome this limitation, we have developed the STZ diabetic primate model, which allows for the study of T2D cognitive impairment without the presence of retinopathy. Interestingly, we observed differences in the cognitive performance between STZ diabetic monkeys and nondiabetic monkeys. These differences were more pronounced in males than in females, suggesting that gender may influence the manifestation of T2D cognitive impairment. In addition, we observed differences in the cognitive performance between STZ diabetic monkeys and nondiabetic monkeys, suggesting that gender may influence the manifestation of T2D cognitive impairment. In conclusion, the STZ diabetic primate model provides a valuable tool for the study of T2D cognitive impairment, allowing for the investigation of the mechanisms underlying this condition without the confounding effect of retinopathy. This approach may have important implications for the development of novel therapeutic strategies for the treatment of T2D cognitive impairment.
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 micropertimetry 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 commented 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 Hegedus
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 (psychoses, 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.

DOI: 10.1530/endoabs.56.PL7

Metabolic control of longevity
PL7

Anti-obesity effect in mice and monkeys of partial inhibition of PI3Kα
Manuel Serrano
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 therefore 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.

DOI: 10.1530/endoabs.56.PL7
Symposia
Predicting events in autoimmune thyroid disease

S1.1 The THEA score in familial thyroid dysfunction. Predictive factors of autoimmune thyroid disease
Grigoris Effraimidis
Denmark.

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 hypothyroidism 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
Luca Chiavato
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. Lymphoplasmacytic infiltrate, storiform fibrosis and obliterator 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

New scores for the prediction of Graves’ disease
Milosˇ Zarkovic´
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 disease. 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 thyroid (FT4) concentration, thyrotropin-binding inhibitor immunoglobulin (TBI) 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), TBI 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.

DOI: 10.1530/endoabs.56.S1.3

Salt & Sweet

S2.1 Hyponatremia and mortality: moving beyond associations
Ewout Hoorn
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.

DOI: 10.1530/endoabs.56.S2.1

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.

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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, TMA, 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 TMA 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 TMA (gTMA) 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 acids 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.

DOI: 10.1530/endoabs.56.S3.1

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 (T4) levels 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 this condition is individual. Some persons with subclinical hypothyroidism is stable in trials, or to follow serum TSH values, which should normalize spontaneously. If TSH levels exceed 10 mU/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...
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 adulthood

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 activated by high-fat diet), can drive an exaggerated transcriptional response to specific transcription factors, such as the transcription factor EGR-1 (which is activated by high-fat diet in EGR-1 target genes). 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 contaminants and endocrine disruption: the story of obesogens

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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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Iodine deficiency in pregnancy and development of offspring

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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, gial development and myelination 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 decrease in frequency of moderately severe 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.

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The role of sperm epigenome in fertility and inheritance

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 germ-line-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

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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).

References

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S6.2

Genetics can help to improve precision medicine in diabetes

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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) (Abhary 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 (MOB) 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.

DOI: 10.1530/endoabs.56.S6.2

S6.3

Precision Nutrition in Obesity: gene-diet interactions

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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.

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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. 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 metabolism of the invertebrate amphibians. However, T3 is incapable of stimulating the TH receptor in amphibian in vitro, in contrast to the potent stimulation by 3,3',5-triiodothyro-acetic acid (TriaC). Furthermore, a deiodinase has been characterized in amphibians, which is inactive towards iodothyronines but effectively deiodinates TriaC. Together, these findings suggest that TriaC is the active TH in amphibians. 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 established. 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-triiodothyropruvic 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 defects. 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 patients.

References
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S7.2
Tetrac as an antiangiogenic agent in cancer
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Germany.

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 tetracriodothyroacetic 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 radiodide uptake, measured by iodide-124 PET, demonstrated successful tumoural recruitment of MSCs followed by VEGF promoter-driven NIS expression. In hyperthyroid animals, tumoural radiodide 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
Paul Yen
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 hypertriglyceridaemia 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.

DOI: 10.1530/endoabs.56.S7.3
Bone fragility – from bench to clinic
S8.1
Clinical spectrum of new monogenic forms of osteoporosis
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Finland.

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 post translational 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 bone mass.

S8.2

Abstract unavailable.

S8.3

Hypophosphatasia – diagnosis and treatment
Lothar Seefried
Germany.

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 (Pi), 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 unspecified 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 it 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,XXX karyotype, the most frequent male chromosome disorder. Yet the incidence of the syndrome is probably significantly higher than the diagnosed cases 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 early intervention may be 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, in male, 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.

DOI: 10.1530/endoabs.56.S9.2
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±8.8 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, both HO and CO were independently associated with a higher incidence of MACE (HR=1.05), when compared to the rest of the sample.

Conclusions
Our data suggest that healthy obesity induces subclinical ED and prostatic inflammation when compared to normal weight subjects. Conversely, no differences in seminal parameters among groups were observed. Finally, the HO showed higher risk of ultrasound and biochemical (semen IL-8) features of 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).

Abstract unavailable.
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.

DOI: 10.1530/endoabs.56.S11.2

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 2009, 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 penumbra 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 radiation 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.

DOI: 10.1530/endoabs.56.S11.3

S12.1

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

Abstract unavailable.

S12.2

Bone quality evaluation in Pituitary diseases
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The Netherlands.

The skeleton consists of cortical bone and trabecular (cancellous) bone. Cortical bone, which comprises 80% of the skeleton, is designed to provide rigidity and strength and is predominantly found in the long bones, e.g. at the femur. Cancellous bone has a more flexible design with interconnecting trabecules, 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
Jens Bollerslev
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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**$13.3$**

**Browning of adipose tissue in humans**

**Piijo Nuuttila**

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. Therapeutic activation of BAT 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 obese increases after bariatric surgery. Chronic cold exposure for 6 weeks at 17°C during 2-hour per day resulted 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 long intervention. Irsin 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 all adult humans and not only obese individuals is still being constantly. Recent studies have suggested a link between VAT 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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**$13.2$**

**Adipose tissue browning in mice and men**

**Florian Kiefer**

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 thermogenic potential of adipocytes. Two distinct strategies are currently being pursued: one is the activation of brown fat, 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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**$13.1$**

**The colours of fat**

**Brown adipose tissue as an endocrine organ**

**Francesc Villarroya**

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 transplanted 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 secreto. 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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**$14.1$**

**Developmental wiring of GnRH neurons**

**Ulrich Bochm**

Germany.

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 utoero, 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 (hp-g) 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 utoero. 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 agglasia, with congenital hypogonadotrophic 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), FGFR8 (fibroblast growth factor 8), PROKR2 (prokineticin receptor 2), FGFR2 (fibroblast growth factor receptor 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., signalings by FGFRs 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 hypermethylation 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 findings demonstrate the central role of mitochondrial deficiencies in the predisposition to paragangliomas.

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S15.4

Abstract unavailable.
S15.1

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S15.2

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S15.3

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 SFI. 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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S15.4

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S15.5

Abstract unavailable

S15.6

Changing practice in the management of thyroid neoplasms

S16.1

New steps in the genomic alterations of thyroid malignancies

Garcilaso Riesco-Eizaguirre
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 Atlas (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 IncRNAs 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. I.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

Endocrine Abstracts (2018) Vol 56
S17.2 Genetics of Primary Bilateral Macronodular Adrenal Hyperplasia: when and what to test
Rossella Libè
France.

Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) consists of bilateral development of adenocortical 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 Lymphomatosis 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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Greece.

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 ≤ 50 nmol/l (1.8 μg/dl) exclude ‘ACS’, values of > 140 nmol/l (5 μg/dl) confirm ‘ACS’ and values between 50 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 helpful. Screening for adrenal insufficiency may be performed in a subset of 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.

 DOI: 10.1530/endoabs.56.S17.3

Borderline testosterone and metabolic outcomes among sexes: clinical relevance
S18.1
Sex hormones, obesity and type 2 diabetes-is there a link?
Alessandra Gambineri
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
Mirjana Sumarac-Dumanovic
Serbia.

Although there are many phenotypes of polycystic ovarian syndrome (PCOS), we mainly talking about three phenotypes: metabolic, hyperandrogens 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 progesterone is an also reasonable alternative.

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Endocrine Abstracts (2018) Vol 56
Cytoskeleton, pharmacologic resistance and clinical aggressiveness in pituitary tumours
Giovanna Mantovani
Italy.

Pituitary tumours, 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 tumours since they mediate inhibitory effects on both hormone secretion and cell proliferation, and their expression is retained by most of these tumours. Although long acting DA and SS analogs are currently used in the treatment of prolactin (PRL)- and growth hormone (GH)-secreting pituitary tumours, 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 tumours 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/signalling. In particular, we demonstrated a role for cytoskeleton protein filamin A (FLNA) in DRD2 and SSTRs expression and signalling in PRL- and GH-secreting tumours, respectively, first revealing a link between FLNA expression and responsiveness of pituitary tumours to pharmacological therapy. Moreover, another cytoskeleton actin binding protein, cofilin, was shown to be a determinant of invasion and new biomarker of pituitary tumoral invasiveness. In this respect, we recently showed that invasiveness of pituitary tumours 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.

DOI: 10.1530/endoabs.56.S18.3

How can treatment effects your pituitary
Frederique Albaré
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 ± s.d.) after treatment start, occurring in 66% after the third infusion. The main initial symptoms were headache (n=13) and asthma (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 recommendations about follow-up and treatment. DOI: 10.1530/endoabs.56.S19.3

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. DOI: 10.1530/endoabs.56.S20.1

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, hypertriglyceridemia, 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 drag 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. DOI: 10.1530/endoabs.56.S20.2

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 dyslipidaemia. 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. DOI: 10.1530/endoabs.56.S20.3

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 Meczkański
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 spontaneous abortion than healthy women. Numerous studies reported that glucocorticoid treatment can lower the risk of spontaneous abortion. Males with CAH also may present impaired gonadal function and infertility. CAH patients with fertility problems should be consulted and properly treat. DOI: 10.1530/endoabs.56.S21.3

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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.

DOI: 10.1530/endoabs.56.S22.2

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 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.

DOI: 10.1530/endoabs.56.S23.3

Ups and downs of hypothalamo-pituitary hormones

How Does Pituitary Release its Hormones?

Patrice Möllard

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...
TNF-alfa in hypopituitary and control subjects - these studies showed that HP gland during metabolic stress we have compared metabolic responses to LPS and decreasing protein breakdown and urea formation. To test the role of the pituitary increase endogenous glucose production and (iv) GH preserves protein by overall catabolism and increased levels of lactate and ketone body stress and a more slow component, driven by cortisol and GH, both being characterised stress hormones, suggesting that the thermoregulatory unit in the preoptic part of pyrogens (fever), exercise or heating with hot water, initiates hypersecretion of hormones are uncertain. An increase in body temperature, whether induced by endogenous pyrogens'). The exact mechanisms triggering the release of stress (adrenaline, glucagon, cortisol and growth hormone(GH)) and mobilisation of all conditions generate a metabolic stress response with release of stress hormones. In general these 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/oligosaccharide (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 the 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. DOI: 10.1530/endoabs.56.S24.3

Late Breaking

**S25.1**

Extracellular Vesicles: from waste-containers to new opportunities

Francesc E. Borrás

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. DOI: 10.1530/endoabs.56.S25.1

**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 antiapoptotic effects in *in vivo* 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 MA/602 and MA/690, either alone or in combination with chemotherapeutics, 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. DOI: 10.1530/endoabs.56.S24.2

**S24.3**

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

Niels Møller

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, glucose, cortisol and growth hormone(GH)) and mobilisation of all major fuel sources - lipids, protein and carbohydrate. In addition bacterial ingredients (eg endotoxin/oligosaccharide (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 the 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. DOI: 10.1530/endoabs.56.S24.3
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.

DOI: 10.1530/endoabs.56.S25.3

Cortisol: Too much of a Good Thing

S26.1

Genetics of Cushing’s disease

Laura C. Hernández Ramírez
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. Today, genetic testing for 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 corticotrop 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.

DOI: 10.1530/endoabs.56.S26.1

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.

DOI: 10.1530/endoabs.56.S26.2

S26.3

Differentiating Cushing from Pseudo-Cushing

Krystallena Alexandraki
Greece.

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 hypercortisolism 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), dexmethylasone 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.

DOI: 10.1530/endoabs.56.S26.3
Emerging treatments in osteoporosis
S27.1

Abstract unavailable

Novel therapies: PTH-related protein and sclerostin inhibition
Tilmann Rachner
Germany.

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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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 antiresorptive (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, whereas they are ‘ingested’ by osteoclasts and promote osteoclast apoptosis. BP can provide additional BMD 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-naive 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 antiresorptive 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.

DOI: 10.1530/endoabs.56.S27.3

Endocrinology Meets Immunology
S28.1

Abstract unavailable

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, hypopituitarism 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.

DOI: 10.1530/endoabs.56.S28.3
**S29.1**

**Thyroid hormone action: regulation and clinical implications**

Balázs Gereben

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 hypothalamic 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 tanyocytes, 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 hypothalamic-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.

DOI: 10.1530/endoabs.56.S29.1

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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 ≥91 years and women ≥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/T3 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.

DOI: 10.1530/endoabs.56.S29.2

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**S29.3**

Abstract unavailable.

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**S30.1**

**Disorders of Sexual Development (DSD)**

Abstract unavailable.

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**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 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 viable 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.

DOI: 10.1530/endoabs.56.S30.3

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
Karín Amrein
Austria.

Depending on definition and population, vitamin D deficiency (usually 25(OH)D ≤ 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 last 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 beneficial 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 1α-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 imubes 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
Alber to Per eira
The Netherlands.

The mission of the European Reference Network on Rare Endocrine Conditions (Endo-ERN) is to reduce and ultimately abolish inequalities 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 helpdesk 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 Bro’samle, Endo-ERN ePAG
Manuela Bro’samle
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 LIM3, 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 CTNNDD2. 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.

References

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NSA3

Reprogramming 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 lifelong 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 through 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.

DOI: 10.1530/endoabs.56.NSA3

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 Iiga
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 plasma/serum or from extracellular vesicles. The miRNA
yield of whole plasma 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.
DOI: 10.1530/endoabs.56.NSA5
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 cornerstone. Although challenged during recent years by means of being insensitive and invasive, it remains the gold standard method for localization 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 current 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 of 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.

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Subclinical hypothyroidism is a disease

D3.1

FOR – subclinical 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 imply 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 under 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 as 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 cannot 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.

DOI: 10.1530/endoabs.56.D4.1

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-dependent. 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 gonadotropin 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

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 WHODPCP definition and can be

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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.

DOI: 10.1530/endoabs.56.D6.2
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 optional 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. Reaching 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 prevention 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, lanreotide 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, multit gland 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.

DOI: 10.1530/endoabs.56.MTE2

MTE3

Managing delayed puberty
Taneli Raivio
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.

References and recommended reading

DOI: 10.1530/endoabs.56.MTE3

MTE4

Osteoporosis in men: management of bone health in the endocrine outpatient clinic
Dirk Vandenbroucke
Belgium.

Several wrong conceptions persists 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 despite 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 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.

DOI: 10.1530/endoabs.56.MTE4

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 disease (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. Hypoglycaemia, 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 hypoglycaemia-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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MTE8
Hormone replacement for the travelling patient Tina Dusek, 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 hypoglycaemia. Westward travel means a longer day, and so 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 hypoglycaemia. Westward travel means a longer day, and so insulin doses are unnecessary if patients are crossing fewer than five time zones.

DOI: 10.1530/endoabs.56.MTE8

MTE7
Difficult cases of differentiated thyroid cancer Emese Mezosi 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 subgroup of 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 node mets with rapid progression.

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MTE9
Premature ovarian insufficiency: an endocrine perspective Svetlana Vujovic 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 disorders and disturbing quality of life. Infertility in POI represents a special issue. Hypoestrogenism, hypoprogesteronism, hypoandrogenism, decreasing of dehydroepiandrosterone 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

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cardiovascular disease. Osteoporosis, joint stiffness, 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, especially 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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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 evidence, PCSK9 inhibitors, although homoygous 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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MTE10
The effect of gender-affirming therapy on bone in transgender persons
Guy T’Joen
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 osteopenia, 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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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 from 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 appendectomy 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
Mario Maggi
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 lesser 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 end-point. 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?
Stefan Pilz
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 extraskelatal 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 ≥ 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
Nigel Glynn
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.

DOI: 10.1530/endoabs.56.MTE15

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 incidentalomas 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 specialties during radiological investigation. Large retrospective series reveal that the vast majority of adrenal incidentalomas 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 Rizzotti
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, allowing reconstitution of cellular hierarchies, and sometimes resolution to the cell(s) of origin of the tumour. This may be 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 offers 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.

DOI: 10.1530/endoabs.56.MTBS2

**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 TRa 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
Abstract unavailable.

Nursing Management of Congenital Adrenal Hyperplasia (CAH): Education, Management 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 psychosocial 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 initially for parents and child as they grow through adolescence to adulthood 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 psychosocial education program (CAHPEP) for families and patients with CAH, is now a website titled ‘CAHPePTalk.com’, with translations in Vietnamese, Bahasa-Indonesian and Urdu-Pakistan, with the support of Caring Living As Neighbours (CLAN), APPES & APEG.

DOI: 10.1530/endoabs.56.N3.1
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
Alina Rozanska
Poland.

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 patients 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.

DOI: 10.1530/endoabs.56.N4.4

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 kg), nausea, and vomiting. Thyroid function test revealed thyrotropinocysis with increased T3 = 8.3 ng/dl (2.4–4.1 ng/dl) and free T3 = 2.3 ng/dl (0.8–1.3 ng/dl) concentrations and low TSH (< 0.05 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 without anti-TSH receptor antibody. Thyroid ultrasound showed a normal-sized gland without hyper-vascularization.

Results
DNA sequencing of this woman and her mother, led to identify a heterozygous variant (c.1789 C > 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 gonadotrophin.

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 transmembrane 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 hypersensitivity to HCG and LH in women of this family.

DOI: 10.1530/endoabs.56.OC1.1

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 these 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 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, induction of delivery, cesarean 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 (2.7%) 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 (23.9%). There were no significant differences in the weights of the newborns of group A (3186 ± 515 gr), B1 (3229 ± 440 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 ± 5.5. The mean age of pregnant women in group A was 33 years ± 5.04, B1 31.95 ± 5.22 and B2 31.95 ± 5.38. 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.

DOI: 10.1530/endoabs.56.OC1.2

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 trials (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, I² 21%), symptoms of depression (three studies, SMD = −0.14, 95%CI −0.41 to 0.12, I² 0%), and cognitive function (four studies, SMD 0.11, 95%CI −0.09 to 0.32, I² 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, I² 0%), and 13 evaluated the body mass index, again showing no benefit (−0.02 kg/m², 95%CI −0.40 to 0.36 kg/m², I² 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.
Iodine prophylaxis based on iodization of household salt is effective in reduction of thyroid volume in childhood.

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. The study was approved by the Scientific Ethics Committee of the Jagiellonian University.

The impact of sex, ultrasonographic thyroid autoimmunity features, gender, UIC and date of birth (before vs. after introduction of obligatory iodine prophylaxis) were considered as potential confounders. UIC was measured by Sandell-Kolthoff method.

The median standardized thyroid volume (TVs) was 3.96 ml/m² (LQ – 3.12 ml/m², UQ – 4.91 ml/m², respectively). The median standardized thyroid volume (TVs) was measured by ultrasound (7.5 MHz Linear probe) and calculated according to the following formula: weight (kg)0.425 * height (cm)0.725 * 7.18 * 10^-4. TVs were compared between children born before (after) introduction of iodine prophylaxis by Mann-Whitney test.

The impact of age was evaluated with linear regression model.

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.

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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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

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.

DOI: 10.1530/endoabs.56.OC1.5
Kiss1 mRNA level was correlated with the serum AMH levels (expression of mRNA level was correlated with the follicular number (P did not show significant difference between the PCOS group and normal
Tacr3 (BMI oocyte maturation rate and circulating hormones levels, including E2, progesterone, follicle-stimulating hormone (FSH), luteinized hormone (LH), were measured with the radioimmunoassay method. We found that Kiss1 mRNA expression 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 & method
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/CGR, 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 steroidogenesis 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.
DOI: 10.1530/endoabs.56.OC2.1

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<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 E2, progesterone, follicle-stimulating hormone (FSH), lutinized hormone (LH), and E2, progesterone, LH levels in HCG day. Kisspeptin-10 significantly inhibited the expression of MMP9 and COX2 in a dose-dependent manner, which were antagonized by kisspeptin antagonist, P234. Kisspeptin-10 also significantly upregulated the expression of Tac3. Senktide, an agonist of TAC3, 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.
DOI: 10.1530/endoabs.56.OC2.2

OC2.3
Whole exosome 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 FA gene in the brother of the index case and in 27 selected NOA patients was performed. DEB-induced chromosome breakage 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 FA 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 findings highlight 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, normospermic men.
DOI: 10.1530/endoabs.56.OC2.3

OC2.4
Novel role of central ceramide signaling in mediating obesity-induced precocious puberty
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Objectives
1. To compare effects of the maturation triggers hCG, GnRHs 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/CGR 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 steroidogenesis 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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OC2.5
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 naive, overtly hypothyroid, consenting male patients were included. Hormones assessed were free T₄, free T₃, thyroid stimulating hormone, follicle stimulating hormone (FSH), lutetizing 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), 67.5% had low total sperm motility, 72.9% 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.

DOI: 10.1530/endoabs.56.OC2.5
Can a bone protein protect against muscular dystrophy?

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Receptor-activator of nuclear factor κB (RANK), its ligand RANKL and the soluble decoy receptor osteoprotegerin (OPG) are key regulators of osteoclast differentiation and bone remodelling. Although there is a strong correlation between osteoporosis and skeletal muscle atrophy, the functional relevance of a particular biological pathway that regulates synchronously bone and skeletal muscle physiopathology remains elusive. We thus hypothesized that RANKL/OPG, which is a key pathway for bone regulation, is involved in Duchenne muscular dystrophy (DMD) pathophysiology. Our results show that muscle-specific RANK deletion (mdx-RANKmko) in dystrophic 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 anti-TRAIL antibodies to decipher the dual function of OPG.

Objective 1: To elucidate the role of RANKL/OPG in skeletal muscle and bone homeostasis.

Objective 2: To determine the efficacy of RANKL/OPG inhibition on muscular dystrophy.

Conclusion

Can a bone protein protect against muscular dystrophy?

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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 BAT contributes to systemic energy homeostasis.

Objectives

Assess [18F]-FDG uptake into bone marrow adipose tissue (BMAT) in healthy humans.

Methods

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

OC3.3

(18F)-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 [18F]-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 U/kg) or saline (10% NaCl 0.45%). Animals were immediately injected with [18F]-FDG and imaged immediately (RT) for 1h before scanning. Objective 2: prior to [18F]-FDG administration mice were fasted for 4h at RT (control) or 4°C (acute or CC), with CC mice further housed at 4°C for 72 h before imaging. Objective 3: human subjects were exposed to mild cold (16°C) for 2h before [18F]-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 [18F]-FDG skeletal uptake. Insulin-stimulated [18F]-FDG uptake in the femur and the heart, as previously reported, but did not affect [18F]-FDG uptake in the bone or MC at other skeletal sites. Despite suggestions that BAT contributes to insulin resistance and cold exposure, CC exposure profoundly increased [18F]-FDG uptake in many of the tissues analysed. In cold-exposed humans, [18F]-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 [18F]-FDG uptake into the bone and had no effect of [18F]-FDG uptake in 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.

OC3.4

Renal function change in chronic hypoparathyroidism patients treated with recombinant human parathyroid hormone (1-84) (rhPTH1-84) 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, hyperparathyroidism, 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 had concomitant nephrotoxic drug use or a history of hypercalcemia, hyperparathyroidism, 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 ± 2.96 (p < 0.001) in the rhPTH1-84-treated vs ST-only 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 m²; 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 m²; 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.

DOI: 10.1530/endoabs.56.OC3.4
Novel insights into prediabetes and type 2 diabetes

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 novel (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-T2D 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-T2D and non-T2D patients after 3 years of follow-up under the different dietary 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 incident-T2D and non-T2D subjects, as several spliceosomal components (e.g. SPQ 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. RNA4 and RNA11) 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 1.02, 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, HbA1c, 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 PWV, 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 was 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/db 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) andITT (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 hyper trophy 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 m², 10-year Framingham score ≥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).

For non-CKD patients, we assessed the incidence of CKD (decrease in eGFR ≥50% to <60 ml/min per 1.73 m²) 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

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 as an HbA1c between 5.7 and 6.5%. The spirometric parameters were evaluated according to the global initiative for chronic obstructive lung disease.

Conclusions
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 (FEV1; 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 FEV1 <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; FEV1: 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 (R²=0.082, β=-0.062) and FEV1 (R²=0.073, β=-0.055).
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 95.3%, 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 diameter) 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 pmol/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 1-24 ACTH 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 adrenalectomy SH vs NS (n = 175) and hyperplasia SH vs NS (n = 132). 1-24 ACTH 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 adrenalectomy associated with SH vs NS. Steroid profiling after 1 mg-DST revealed higher levels of cortisol, 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) 1.000–1.251, 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, β1, β2 and RIIα, β1, β2, IIIα, IIIβ, 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 PKRACA have been found in 30–40% of cortisol-producing adrenocortical adenomas (CPA). We recently described reduced levels of RIIB in PKRACA-mutated CPA compared to PRKACA WT CPA. In NCI-H295R cells co-transfected with RIIB and CαWT or Cα2208D, the L206H mutation led to a full degradation of RIIB and this degradation could not be reversed by proteasome and lysosome inhibition but by caspase inhibition. Same co-transfections with RIIα did not lead to its degradation. When the inhibitory site of RIIB was replaced by the corresponding amino acids of RIIα, Cα2208D did not lead to RIIB degradation, while it was able to degrade RIIB when its inhibitory site was replaced by the corresponding amino acids of RIIB. Same results were observed...
Assessment of Tissue Sodium Content by 23Na-MRI in Patients with Adrenal Insufficiency – a Pilot Study

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Introduction

Patients with chronic primary adrenal insufficiency (PAI) depend on lifelong glucocorticoid (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 23Na-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 23Na-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 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 23Na-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

<table>
<thead>
<tr>
<th>Tissue SC (mmol/l)</th>
<th>Subtherapeutic</th>
<th>Optimal</th>
<th>Supraphysiological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle-SC</td>
<td>17.27 ± 5.15</td>
<td>19.21 ± 2.12</td>
<td>20.96 ± 0.44</td>
</tr>
<tr>
<td>Sòrin-SC</td>
<td>15.12 ± 3.25</td>
<td>16.08 ± 0.03</td>
<td>18.41 ± 3.09</td>
</tr>
<tr>
<td>MC replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle-SC</td>
<td>18.09 ± 2.44</td>
<td>19.01 ± 3.17</td>
<td>20.91 ± 0.5</td>
</tr>
<tr>
<td>Skin-SC</td>
<td>15.06 ± 2.14</td>
<td>15.22 ± 2.3</td>
<td>18.94 ± 3.95</td>
</tr>
</tbody>
</table>

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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.gov.2009-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 (22.3; 29.4) kg/m²; 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 (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/m²), 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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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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OC6.2 Deep transcranial magnetic stimulation acutely modulates neuro-endocrine pathways underlying obesity
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Deep Transcranial 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 dysfunctional role of FPC 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 known. Aim of this study was to investigate the effects of a single dTMS session on neuro-endocrine pathways in obesity. Forty obese patients (11 M, 29 F; age: 48.0 ± 2.1; 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 ofnorepinephrine was found (5.6 ± 0.9 vs 6.5 ± 1.2 ng/ml; +18.0 ± 6.8%; P = 0.01), a rise in β-endorphins levels was also shown (0.338 ± 0.049 vs 0.372 ± 0.048 ng/ml; +13.9 ± 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 ± 1.8%; P = 0.002), whilst leptin levels significantly decreased (66.9 ± 10.5 vs 56.3 ± 9.0 ng/ml; −16.3 ± 2.0%; 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 mU/ml; −20.7 ± 4.7%; P = 0.001) and prolactin (17.1 ± 1.3 vs 10.6 ± 2.8 ng/ml; −34.7 ± 4.7%; P < 0.0001). In the LF, a significant reduction of salivary cortisol was also observed (29.4 ± 2.9%; P = 0.015). These results suggest that dTMS can acutely affect oxyrenergic 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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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=49), primary macronodular adrenal hyperplasia (PMAH, N=3), and primary pigmented micronodular dysplasia (PPNAD, N=Cushing’s disease (CD, N=1)) were included. ACAs secretion was either cortisol (N=9), no secretion (N=47), mild cortisol secretion (N=6), or aldosterone (N=6). Transcriptome, methylene, miRNome and mutational status were generated using Affymetrix U133plus2, Illumina Infinium 27k, Illumina sequencing or Life Technologies ampliseq targeted NGS respectively.

**Results**

Four main molecular groups were identified by transcriptome, methylene, 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 steroidogenic enzyme associated, including CpG island hypomethylation in tumors with or no mild cortisol secretion, miRNA specific patterns in different subgroups, and direct regulation of steroidogenic enzyme expression by methylation.

**Conclusion**

This first large-scale pan-genomic 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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**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 to −0.13) lower 25(OH)D. VAT was inversely associated with serum 25(OH)D concentrations in both men and women. 1 cm2 higher VAT was associated with 0.05 nmol/l (−0.09 to −0.02) lower 25(OH)D in men, and 0.06 nmol/l (−0.10 to −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 (−10.2D to −7.73) 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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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 carcinomas (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 using generalised 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 ACA 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 AUCROC 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 adrenalectomy. 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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OC7.4
Germline mutations in the mitochondrial 2-oxoglutarate/malate carrier (SLC25A11) gene confer predisposition to metastatic paragangliomas
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Integrative genomic studies of paragangliomas (PGL) have shown that PGL susceptibility genes are the main drivers of tumorigenesis. Comprehensive genetic analyses have identified germline SDH mutations and, to a lesser extent, FH gene

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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 incProfilers® qPCR Array with SYBR® green detection of 90 LncRNAs in a preliminary set of 4 parathyroid carcinomas (PCAs), 12 parathyroid adenomas (PDAs) compared with 2 normal parathyroid glands (PaGs), SAM significance analysis identified 9 differentially expressed LncRNAs: 3 LncRNAs were upregulated in PCAs (BC200, HOXAX-AS, WT1-AS), 4 LncRNAs were downregulated in PDAs (HARI8, HOXAX-AS, MEG3, NEAT1) and 2 downregulated in both PDAs and PCAs compared to PaGs (KCNO1/OTT, SNHG6). The 9 LncRNAs were validated in a second independent series of parathyroid samples including 7 PCAs, 6 atypical PaGs, 26 PDAs and 4 PaGs. Unsupervised analysis of the LncRNAs expression levels in this set of 40 parathyroid samples, identified three clusters: cluster 1 was characterized by LncRNAs general downregulation, cluster 2 showed LncRNAs diffuse upregulation, while cluster 2 presented an intermediate pattern. Cluster 2 included all the 4 PaGs and a subset of PDAs, whereas clusters 1 and 3 included PCAs, atypical PDAs and the remaining PDAs. 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%) PaNs and loss of 1p in 7 (27%) PaNs. MEN1 mutations were detected in 5 PDAs, while CDC73 was mutated in 4 PCAs. Interestingly, chromosome 11 monosomy and MEN1 mutations were more frequent in cluster 2 PDAs; cluster 1 included most PaNs and 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 PDAs with downregulated MEN1 mRNA levels had low KCNQ1OT1, NEAT1 and SNHG6 expression levels, suggesting an epigenetic role for menin. Experiments aimed to invest the effect of MEN1 silencing on the MEN1-associated LncRNAs are ongoing. In conclusion, parathyroid tumors show genetic and epigenetic heterogeneity affecting clinical presentation.

DOI: 10.1530/endoabs.56.OC7.3
Background Administration of α-adrenergic receptor antagonists is recommended before resection of a phaeochromocytoma (PCC) in order to prevent perioperative cardiovascular complications. For this purpose either phenoxbenzamine (PBX) or doxazosin (DOX) is commonly prescribed. We conducted the first randomized controlled trial comparing the efficacy of PBX and DOX in controlling perioperative hemodynamics in patients undergoing PCC resection (ClinicalTrials.gov: NCT01370908).

Methods
Patients ≥18 years with benign PCC were randomized to pretreatment with PBX or DOX. Preoperative BP targets were: <130/80 mmHg (systolic) and <90–110 mmHg (upright). β-blockers were added if heart rate was >80/min (systolic) 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 PBX (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 PBX, respectively (P = 0.002). Intraoperative time outside BP target range was 12 (5–20) % in the DOX group and 11 (4–21) % in the PBX 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 PBX 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 PBX group (P = 0.005). The number of intraoperatively administered isotonic/vasopressor agents was 0, 1 or ≥2 among 18, 40 and 42% in the DOX group, respectively. Respective percentages in the PBX 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 and 55 (0–660) μg in the PBX group, respectively (P = 0.98 and P = 0.59).

Conclusions
The results of this RCT demonstrate an equal efficacy of DOX- and PBX-pretreatment in intraoperative hemodynamic control during PCC resection. Patients pretreated with PBX required more β-blockers preoperatively, presumably via enhanced reflex tachycardia, but fewer vasodilating agents during surgery.

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MicroRNAs as biomarkers in endocrine diseases

MicroRNAs are small (18–22 nucleotides) non-coding RNA molecules that are involved in post-transcriptional gene regulation. They play a key role in various biological processes, including proliferation, differentiation, and development. In the context of endocrine diseases, microRNAs (miRNAs) have been extensively studied as potential biomarkers.

Since 2004, miRNAs have been recognized as regulates in a variety of endocrine disorders, including pituitary adenomas, Cushing’s disease, and thyroid disorders. They have been found to be altered in these conditions, providing insights into disease mechanisms and potentially serving as diagnostic or prognostic markers.

Recent studies have highlighted the potential of miRNAs as biomarkers in endocrine diseases. For example, miR-15a, miR-16, and miR-145 have been associated with the presence of metastatic disease in various tumors, including paragangliomas. These miRNAs have been shown to be upregulated in tumor tissues compared to normal tissues, suggesting their potential as diagnostic markers.

Moreover, miRNA expression patterns have been found to be different between patients with different types of endocrine disorders. For instance, miRNA expression profiles have been compared in patients with Cushing’s disease and those with ACTH-ectopic Cushing’s syndrome. These studies have identified significant differences in miRNA expression between the two groups, indicating potential biomarkers for these conditions.

In conclusion, microRNAs are promising biomarkers in the field of endocrinology. Their role in disease diagnosis, prognosis, and monitoring is expected to increase with further research and validation. However, further studies are needed to fully understand their potential and limitations as biomarkers in endocrine disorders.
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 CYP1B1 (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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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 INDIGO1APP-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 multinominal regression models. Additionally, miRNA and proteins, both separately and together, were used to predict whether individuals belonged to the GO group. 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, bacteriolysis of epithelial cells, complement and coagulation cascades, longevity regulating pathway, miRNA 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 we measure 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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OC9.5
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 non-T2DM 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 non-T2DM group (P < 0.0001). Non-T2DM patients without fractures had significantly higher mobility scores (P < 0.01) as compared to non-T2DM patients with fractures or the respective T2DM groups. Vitamin D levels were different between non-T2DM with- and without fracture (P < 0.01) but not between the T2DM and the non-T2DM 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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OC9.9
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 administered 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 (Tn/VBV) 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 with murine osteoblast 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 initiating sporadic conditions
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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 diet. Iodotyrosine (Dehal1+/−), homoyodothyrosine (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 (µIC; respect to creatinine) and serum total T4 and T3 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 T4 and T3 were similar between groups (on average, 62.4 ± 2.5 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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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 modeling 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 immunhistochemical 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 T4 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
Differenntiated 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 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
Sentinel lymphatic metastases of clinically N0 (cN0) papillary 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 subcapsulary 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 knock out (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/kg/d, po). After 5 weeks, aortas were dissected 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-2 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) hyperlipidaemia and hyperglycaemia, 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 inhibitor).

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OC10.3
ARMC5 variants and risk of hypertension in African Americans: Minority Health-GRID study
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Minority Health-GRID study (MGRID) is a multi-site, multi-disciplinary research study conducted in the US. The objective is to identify factors leading to the high prevalence of obesity and diabetes in minority populations. Genomic (genetic) variants in the ARMC5 gene have been found to be associated with hypertension in African Americans. This study examines the association of ARMC5 variants with hypertension in African American participants in the MGRID study.
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 were 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 = 0.004) 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 hypertension in African-Americans and a set of 16 rare variants associated with hypertension. We recently found that 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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OC10.5
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. Agranulocytosis, 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 (0.26% of the cohort) developed agranulocytosis. 40,551 year of follow-up: incidence rate 9.62 (6.84-13.15) per 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 irereponsive 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 k67 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 (23%), CTNNB1 (17%), NF1 (11%), ZNF37 (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, KDM4A, BRCAI and BRC2). 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 non-CIMP), chromosomal alterations (Noisy or Chromosomal/Quiet) and molecular (Class-cycle and Wnt-betacatenin pathways) profiles. A subset of 72 ACC was studied by targeted measures, including BUBIB-PINK1 differential expression using RT-qPCR and C636 ischemia methylation of 4 genes (PAX3-GSTF1-PYCARD ACC) 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 < 0.0001). 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 < 0.0001). 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-based 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, useful in clinical routine.

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OC11.3

Clinical and histopathological differences between MEN1 carriers and MEN1 phenoxy patients

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare mult tumour syndrome, characterized by the occurrence of parathyroid (PHTP), 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 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/PHTP in mutation-negative, and PA/PHTP/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-penetrating mutations in other genes cannot be entirely excluded.

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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, hypothalamic, and pituitary function impairment, 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); supratentorial extension in 72% vs 33%, P < 0.001, hypothalamic in 41% 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 gonadotropin (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 hypoplasia. 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, FGFR5/KS6, GNRRH/HHR, NELF (NSMF/HH7, GNRH/HHH, WDRL1/HHH1, HHH5/HHH1, LRRQ23, GLU1, OTX2, TACO1/HHH10, TACR3/HH11 genes). In 25 patients (80.6%) different mutations in examined genes were found. In 13 (52%) cases monogenic mutations were identified, 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 Testosterone 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 hypoplastic. 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 nmol/l), patients with mild/ineffective hormone deficiency (mIHH with TTe 3.5–11.0 nmol/l but with low calculated free Te) and in controls with Te >11.0 nmol/l).

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 hypogonadotropic hypogonadotrophic hypogonadism 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/m2 vs mIHH 24.75 Kg/m2).

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

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Late-night salivary cortisol (LNSC) levels in a Phase III study of long-acting pasireotide in patients with Cushing’s disease (CD)
Introduction
LNNSC has shown high sensitivity and specificity for the initial diagnosis of CD and detection of disease recurrence; however, the use of LNNSC to monitor medical treatment of CD is not well established. The results of an exploratory analysis evaluating changes in LNNSC 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 ≤ ULN at month (M) 7 was the primary endpoint, with change in LNNSC an exploratory objective. At each time point, mean LNNSC (mLNNSC) was calculated as the mean of two measurements from single samples collected at 23:00 ± 1 h on the same days as the first two of three 24-hour UFC measurements. UFC and LNNSC samples were analysed at central laboratories by LC-MS/MS.

Results
Mean (±2SE) mLNNSC at baseline was 10.4 (8.2) nmol/l, with mLNNSC > ULN (3.2 nmol/l) in 125 (91.2%) evaluable patients. Mean (95%CI) changes in mLNNSC 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 mLNNSC was greatest in patients with mUFC < ULN at M7 (−5.1 (−8.3, −2.0) nmol/l). Changes in blood pressure (BP) and weight by mUFC and/or mLNNSC 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/mLNNSC response at M7

<table>
<thead>
<tr>
<th></th>
<th>Both mUFC and mLNNSC</th>
<th>mUFC ≤ ULN only</th>
<th>mLNNSC &gt; ULN only</th>
<th>Both mUFC and mLNNSC</th>
<th>mUFC ≤ ULN only</th>
<th>mLNNSC &gt; ULN only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 150</td>
<td>N = 36</td>
<td>N = 5</td>
<td>N = 52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>−10.8 (−16.7, −5.9)</td>
<td>−3.9 (−7.7, 0.0)</td>
<td>−7.4 (−16.6, 1.9)</td>
<td>−12.8 (−39.1, 5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>−10.5 (−16.1, −5.0)</td>
<td>−4.7 (−10.2, 0.0)</td>
<td>−4.6 (−10.7, −0.6)</td>
<td>−16.7 (−29.0, 3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>−5.7 (−9.1, −2.3)</td>
<td>−3.7 (−5.6, 3.4)</td>
<td>−2.0 (−10.7, 6.6)</td>
<td>−4.8 (−8.6, −0.7)</td>
<td></td>
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</tr>
</tbody>
</table>

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

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

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Background
Patients with active Cushings 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 Cushings 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 = 5) and carcinomatous 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 (6.4–15.6) 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 (26 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 ≤ 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 3.3, P = 0.013) and glucocorticoid substitution (RR 2.1, 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/combope 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 (435P/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 3268.88 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) 1.25–2.06), while in NFPA follow-up 2570.70 person-years (median 7.5 years), SMR was 1.38 (95% CI 1.05–1.79).

Conclusions
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 (54.5% before 2008 vs 73.6% 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 (54.95% vs 56.57%, respectively, P = 0.06). 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 not 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. mRNA-later embedded and further processed for evaluation of the expression of 11 genes related to SSA response: SSTR2, SSTR3, AIP, e-cadherin (CDH1), Ki67, Kallikrein 10 (KLK10), arresin beta-1 (ARRB1), ghrelin (GHRIL), intron 1 Ghrelin (in1-Ghrelin), ZAC1

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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. 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 to −0.66; P = 0.000); Hba1c (ES = −0.48%, 95% CI: −0.59 to −0.37; P = 0.000), fasting plasma insulin (FPI) (ES = −5.12 μU/L, 95% CI: −8.99 to −1.22; P = 0.010) and HOMA-β (ES = −0.80, 95% CI: −1.38 to −0.22; P = 0.007), without changes of triglycerideremia, glucose load (2h-OGTT), HOMA-β, 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 HOMA-β. These results suggest that PEG treatment improves glucose metabolism in acromegaly and this effect seems to be independent from disease control.

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, 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 = 0.003).

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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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 T4 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 findindes 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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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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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 for healing, rather than a pro-inflammatory event as currently proposed. 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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OC14.3 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.

Methods

Streptozotocin-diabetes was induced in male NlR4A1-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 tanspyt digests. To study their biosynthetic characteristics, RNA was isolated from circulating PMo sorted from mice after 5 months of diabetes using anti-CD145, CD11b, CD3, CD19, NK1.1, Ly6C, CD11b, and Ly6G; 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/mm2 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 ± 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 glycaemia 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 (1H-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 glycaemic variability and the results of 1H-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 EasyGlu™ software, the measures of glycaemic variability were calculated (standard deviation (SD), continuous overlapping net glycemic action (CONGA), lability index (LI), low blood glucose index (LBGI), high blood glucose index (HGBI), mean of daily differences (MODD), mean amplitude of glycemic excursions (MAGE)). The 1H-MRS of the brain was performed to determine the main spectra of (1H-MRS). However, the relationship between the results of these studies has not yet been studied.

The 1H-MRS of the brain was performed to determine the main spectra of

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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/m²; 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 glycemic 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-1 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-I) 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 pitiuity 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 57.3 ±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 (coefficient = -2.72, P = 0.03) and higher GH level at diagnosis (coefficient = -2.31, P = 0.01) were significant negative predictors of discordance. Neither surgery nor radiotherapy were associated with a significantly increased risk of IGF-1/GH discordance, although a high IGF-1 discordance was more prevalent post-radiotherapy (coefficient = 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 (coefficient = 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×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 hyperglycaemia-related adverse events. Pasireotide-induced hyperglycaemia 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 hyperglycaemia 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, heterogeneous 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 analysis, 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 analysis also showed no CNVs. Afterward, *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.

**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 received radiotherapy and LA-SSA therapy ≤ 4 months. In 14 of 52 patients, somatotroph adenoma tissue 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 ≥ 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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**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 investigate 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 received radiotherapy and LA-SSA therapy ≤ 4 months. In 14 of 52 patients, somatotroph adenoma tissue 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 ≥ 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 adenoma (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 (NFPAs) (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 NFPAs 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 (NFPAs, 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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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 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 (CSOMZ30CIC05) 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 ≥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 40.9% 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 ≥1 post-baseline safety assessment and with ≥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 ≤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 (NCT01177602) where 25% and 26% of patients on the 40 mg (n=65) and 60 mg (n=65) doses, respectively, achieved normalised IGF1 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 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.
**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 preoperatively. They represent only 1–3% of all retroperitoneal masses.

Case report

A 30-year-old woman was referred to the outpatient to evaluate an adrenal mass observed in an abdominal ultrasound 2 years ago. There were no symptoms or family history suggestive of an adrenal tumor.

Physical examination

The patient was a healthy woman with no signs of Cushing's syndrome or Conn's syndrome. The abdominal examination was normal.

Laboratory tests

The serum levels of ACTH, cortisol, aldosterone, and renin were within the normal range. The adrenocorticotropic hormone (ACTH) stimulation test was normal. Serum amine measurements for pheochromocytoma were negative.

Imaging studies

Abdominal CT scan showed a 2 cm nodular mass in the right adrenal gland. The mass was isoattenuating on T1WI and hyperattenuating on T2WI with typical mural enhancement. MRI confirmed the solid tumor nature and excluded any complications like necrosis or hemorrhage.

Operative findings

The tumor was resected laparoscopically. Histopathologically, the tumor was consistent with an adrenal schwannoma. The patient had an uneventful recovery with no complications.

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Estradiol 1502 µg/ml, Progesterone 39.9 ng/ml, hCG 161250 mIU/ml (comparable with pregnancy of 6–12 weeks). Ultrasonography of the abdomen demonstrated a well-circumscribed hypoechoic mass with cystic and necrotic components that measured 32 x 27 mm, dependent of the right adrenal gland. MRI without gadolinium (2nd trimester) showed a 40 x 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 adrenalecctomy was performed under the suspicion of a malignant tumor or a non-functioning pheochromocytoma, in week 22 of gestation. Microscopically, the surgical specimen showed a tumor formed by fusiform cells, with 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 schwannomas 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 schwanna from malignant entities or pheochromocithoma simply base on imaging. In pregnant woman, like our patient, adrenalecctomy 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 x 3 x 3 cm is detected in the abdominal aorto-cava 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 catecholamines and metanephrines were normal. A fine needle aspiration cytology 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 labelolol 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.Ser198Ala*52 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 50% 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.

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

Etotomide 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, hypokalaemia, hypoccalcaemia and symptoms of an upper respiratory tract infection. Post-adrenalecctomy, mitotane, ketoconazole, metyrapon 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 Hydroimidate 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 hypercortisolaemia 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 infecetulous 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 pseudomembranaceae, until she was able to undergo complete adrenalecctomy (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 therapeutic 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 Keap7’s cycle enzyme encoded by the FH gene. Its inactivating mutations increase intracellular levels of fumarate, leading to mitochondrial psoyosyaxia and transcription of genes involved in tumor growth, thus acting as a tumor-suppressor gene. Germline heterozygous mutations in the FH gene have been associated with the hereditary

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leiomymatosi 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/PGL 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 phaeochromocytoma 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/PGL genes showed a splice site mutation in the FH gene (c.555G>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 121I-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/PGL and HLRCC. Both conditions should be routinely screened once diagnosis has been established.

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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 β-oxidation that results in accumulation of very long chain fatty acids (VLCFAs) 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 man 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 asthenoteratopspermia. 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 VLCEA 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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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 past year. Physical examination revealed facial plethora, dorsal fat pad, truncal obesity, and multiple striae. In addition, she had several hyperpigmented macules.

Discussion
We present a case of Cushing’s syndrome revealing CNC due to a novel inactivating PRKAR1A 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 high homonuclear NOE. MRI (right tumor: 2.6/2.1/1.8, 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 19.6 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 X 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 in the extramural arm of right residual adrenal gland and, multiple 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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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 immunonasay (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 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. The cytochrome P450 2W1 (CYP2W1) is an orphan enzyme able to activate carcinogenic acid 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 treatment were collected. Mitotane sensitivity was calculated by comparing the rate of progression 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.

Conclusions

We demonstrated that ACC patients with advanced disease and 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.

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 remission 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). All animals were biometrically and hormonally 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.

Objectives
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 (93.5%) 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 hypothalamic-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 ± 1580 days, P<4.4x10^-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<4.4x10^-10), 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 using specific monoclonal antibodies against the enzymes CYP11B2 and CYP11B1, catalyzing 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 ≥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 80-6 1Mbs 502, rat), and anti-CYP11B2 (clone 41-17B Mbs 1251, mouse), were purchased from Merck Millipore and diluted 1:200 using EnVision Flex Antibody Diluent (DAKO, DUCO). The PA tissue slides were stained along with control samples from healthy adrenal glands using AutostainerLink 48 (DUCO). 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 for treatment response in context with precise histopathological diagnosis.

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GP29

Salivary cortisol and cortisone in Cushing disease – 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 identify 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 dexmethylasone 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 ≥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 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.

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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/24h); 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 5α-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 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 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 5α-reductase activity during TID and to a lesser extent during DR-HC.

Overall, the differential expression of multiple circRNAs and their clinical significance in ACC tissues as revealed by our study suggests that circRNA0066659 is a novel metastatic factor and prognostic marker in ACC, we propose that circRNA0066659 could be used as a potential target in ACC therapy.

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**Adrenal Cortex**

**GP32**

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

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We previously identified mutations in PRKACA, coding for the catalytic (a) 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, S213R, L212, K214insIILR, C200, G214insV, W197R, E249Q, del244-248).

Five out of seven mutants showed reduced binding to at least one of the two tested regulatory subunits (R1a and R1b). 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 CPA 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, G214insV) induced relevant changes in substrate specificity. Among all CPA 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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**GP31**

**Circular RNA circ0066659 functions as a competitive endogenous RNA by spaying 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 circRNA0066659, 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 circRNA0066659 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 circRNA0066659.

**Conclusion**

We hypothesized that circRNA0066659 could be used as a potential target in ACC therapy.

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**GP33**

**Alterations in Clock genes expression in human benign adrenal tumors**

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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 circRNA0066659, 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 circRNA0066659 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 circRNA0066659.

**Conclusion**

We hypothesized that circRNA0066659 could be used as a potential target in ACC therapy.

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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 adrenal adenomas either because of tumor size (n=7) or secretory syndrome (n=9). CLOCK, BMAL1, CRY1 and PER1 genes expression were analysed by 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 no 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 vitro 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), IGF-1 (P=0.01), AMPK (P=0.03) and AKT (P=0.03), 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[BMAL1], CLOCK, BMAL1, CRY1 and PER1 are differently expressed in adrenal adenomas compared to cortisol-secreting adenomas, in the Mann-Whitney test (non-parametric analysis).

Conclusion
Our in vitro 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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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 pPRE5 vector. Transfections are performed in HEK293 cells to study recombiant ARMC5 protein levels by western blot and cell apoptosis using Annexin V 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 to be 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.Phe147tyr 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 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 counselling 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 Cushings

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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 Adrenocortical 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 gene in cortisol dysregulation and PPNAD development.

Methods

Comparison of the transcriptome of PPNAD tissues, normal human adrenals, and H295R adrenocortical 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. Inactivation 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 Cushings 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 overall survival among the patients 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 overall 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 off the lung (NETL) and 29 neuroendocrine tumors of the gastroenteropancreatic system (GEP-NET). Tumor-DNA were isolated from fresh-frozen tumor tissues. Whole-genome sequencing was performed using a read length of 2x100 bp. Survival analysis off the subjects was performed using Kaplan-Meier and Cox regression methods.
GP40

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

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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 alterations 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. Overall survival was generally good in both groups, especially in patients with early stage disease (T1-N0M0: 2-year survival rates of between 88% and 96%). We have not found any relations between gene profile of MEN1 and ARID1A genes and overall survival in both groups of patients.

Conclusion

The overall 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 patients with NET. This raises exciting possibilities for treating this disease in the future.

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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) – non-functional 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/m² and mean adrenal tumor size (ATS) 32.7±9.8 mm) and age matched 32 healthy controls (HC)(mean age 57.6±9.2 years, mean BMI 26.6±4.4 kg/m²). Based on levels of cortisol after 1mg-dexamethasone suppression test AI patients were divided in two groups: <50 nmol/l, 17 with nonfunctional AI (NAI) and >50 nmol/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 (r=0.527, P<0.001), cortisol after 1mg-dexamethasone suppression test (r=0.594, P<0.001) and the ATS (r=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=0.001). Our study shows that patients with (P)ACS exhibit high prevalence of moderate depressive symptoms. The significant and positive correlation between BDI-II 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 multiscaual 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 prevalence 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 by the detection of in genes coding succinate dehydrogenase (SDH) play a role in pituitary tumorigenesis. Furthermore, MEN1 germline mutations have also been identified in patients with 3PAs.

Results

We have demonstrated a significant enlargement of initially benign non-secretng 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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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). Two of them were initially detected in 6 patients and PCC/PGL in 4 cases. Acromegaly was present in 6 cases (3 microadenomas). The remaining patient was a 53-year-old man with diabetes and a 3 cm pituitary macroadenoma. His moyamoya disease required surgery. Patients with prolactinomas received medical treatment with dopamine agonist and one case required surgery because of drug intolerance. Unilateral adrenalectomy was undergone in 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 another 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 SDHB (1p36) mutation in one patient, SDHB exon 1 deletion in one patient, SDHB (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 3PA 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 cancer1. Phaeochromocytoma and paraganglioma (PPGL) are now recognised to be the most heritable tumour, with 40% having a genetic defect. Mutations in the SDH genes are the most frequently implicated genetic abnormalities 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 1H NMR spectroscopy. HRMAS 1H 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 1H NMR spectrum in LCMModel and using tissue water signal as internal standard for absolute concentrations. 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 PGL, 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 metabolic fingerprints of SDH mutated tumours suggests specific metabolic vulnerability and requires further investigation to determine if this vulnerability can be exploited 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.

References

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GP44
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Background
Pheochromocytomas and catecholamine-secreting paragangliomas (PPGL) are rare catecholamine-producing tumors. Due to the rarity, limited data on prognostic 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% (BP95%: 80.1–91.7) and 75.7% (CI95%: 66.7–82.7), respectively. HRR for death or recurrance 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 10Hounsfield Units cut-off value on unenhanced CT imaging is highly sensitive to diagnose phaeochromocytoma: a multicenter study
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The 10 Hounsfield Units cut-off value on unenhanced CT imaging is highly sensitive to diagnose phaeochromocytoma: a multicenter study

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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]. 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 metastatic or persistent 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 normal breast and their potential relationship to obesity and cancer development.

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 (r < 0.01, 5αR1 R² = 0.33 and 17βHSD5 R² = 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, R² = 0.23). When analysing the levels of steroids present in histological normal, distal to tumour breast 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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**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.
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 PCs. Therefore, new therapeutic tools to manage PCs 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, tumoursphere 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), 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 tumoursphere 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.

In vivo studies reveal a potential therapeutic role of the combination of biguanides and statins for the treatment of prostate cancer
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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 FSHb-chain fragments to ablate FSHR expressing cancer cells in vitro and in vivo. Cytotoxicity of 12 different Phor21-FSHb 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 FSHb33-53 fragment with cysteine (Cys) replaced by serine (Ser) (Phor21-FSHb33-53/C/S) displayed dose-dependently the highest specific cytotoxicity towards HEK293-FSHR cells vs. other compounds. Competitive studies with recombinant human FSH (rhFSH, 100 IU/I) significantly decreased the cytotoxicity of Phor21-FSHb33-53/C/S conjugate in HEK293-FSHR cells. In vivo Phor21-FSHb33-53/C/S treatment significantly inhibited growth of HEK293-FSHR xenografts inducing necrosis. The efficacy of Phor21-FSHb33-53/C/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-FSHb33-53/C/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-FSHb33-53/C/S conjugate may provide a novel specific therapeutic lead into the targeted destruction of FSHR expressing cancer cells.

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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 ≥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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**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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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 (±SD) of age, and body mass index was 64.9 ± 10.0 years and 23.2 ± 2.9 kg/m2. 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, 3,921 (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: 1.77–2.62).

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 on caloric replacement through parenteral nutrition (PN). The present study was designed to prospectively evaluate the association of subcutaneous (SAT), visceral (BAT), 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 (1H spectroscopy for MAT). SBS group showed a non-significant decrease in BMD throughout the study, but BMD was lower in SBS0 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±0.19xSIC0 = 0.81±0.57). Values of MAT, SAT, VAT and OC were similar between groups throughout the study. MAT was negatively correlated with SAT and VAT in 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 (R² = 0.09; P = 0.91). IHL was negatively and significantly associated with femoral neck BMD (R² = 0.16; P <0.05) and total hip BMD (R² = 0.27; P <0.05). Moreover, IHL was positively and significantly associated with CTX (R² = 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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Objectives
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
Forty-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 post 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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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\textsuperscript{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 euthanized. Plasma corticosterone and 11-dehydrocorticosterone were measured by ELISA or LC-MS/MS. Bone loss (calcified bones) and BMAT (decalcified, conium-rutexate-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\textsuperscript{Del1/Del1} mice, CR decreased body 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\textsuperscript{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\textsuperscript{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 with hip 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 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 \pm 573 μg/g/l; B-crosslaps values increase with the number of denosumab doses (P < 0.05) and decrease with age (P < 0.001). 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 < 0.001). The mean reasons for DD were: end of AI or no more osteoporosis treatment (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, base-doxifene 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.

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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 data made the registration of a 3D-functional 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% Δ) 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 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 (ADIL1β/IL1β+VD 534 vs 205, P<10−5; HCIL1β/IL1β+VD 307 vs 213, P=2×10−4). 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 (ADIL1β/IL1β+VD 134 vs 126, P=0.7, HCIL1β/IL1β+VD 76 vs 126, P=2×10−3). 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 (ADIL1β/IL1β+VD 12 vs 14, P=0.06, HCIL1β/IL1β+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 response 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 KG, 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 non-diabetics and for rs416473 (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=0.099) in prediabetics and for rs662138 (P=0.034) in T2DM. Associations with IMT were documented in T2DM for rs806383 (P=0.034), rs210837 (P=0.027), rs662138 (P=0.008), as well as for rs12208357 (P=0.030) in prediabetics for rs34130495 (P=0.048) and rs662138 (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 lepton 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 lipolysis, and increases hepatic metabolism 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 for 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 intake of n-3 PUFA, n-6 limonin 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 expression and 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/m². Median intake of n-3 PUFA in our study was 2.44 g/day which corresponded to 0.88% of total energy intake. 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 (β = −0.52, P < 0.001) and visceral (β = −0.78, P < 0.001) adipose tissues. Moreover, we found a significant inverse association of dietary intake of ALA (β = −0.695, P < 0.001) and DHA (β = −0.471, P = 0.009) with leptin gene expression in visceral adipose tissue. There was a significant correlation 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, anti-lipid medication. Before the surgery, a reliable and validated semi-quantitative food frequency questionnaire was completed to assess habitual intake of n-3 PUFA, n-6 limonin 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 expression and 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/m². Median intake of n-3 PUFA in our study was 2.44 g/day which corresponded to 0.88% of total energy intake. 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 (β = −0.52, P < 0.001) and visceral (β = −0.78, P < 0.001) adipose tissues. Moreover, we found a significant inverse association of dietary intake of ALA (β = −0.695, P < 0.001) and DHA (β = −0.471, P = 0.009) with leptin gene expression in visceral adipose tissue. There was a significant correlation 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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GP66

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

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Background

The recently discovered myokinin irisin, a peptide originated by a proteolytic cleavage of the transmembrane protein fibroblast growth factor 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 HFrEF, age range 59–88 years, mean±S.E.M. BMI 28.9±1.3 kg/m²; n = 18 HFpEF, 54–88 years, BMI 26.5±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 H2O2-metmyoglobin and the chromogen ABTS.

Results

The two groups did not show significant differences in NT-proBNP levels (2548±551.1 ng/ml in HFrEF vs 6007.7±2979.2 in HFpEF). Fasting irisin levels were significantly lower in HFrEF (mean±S.E.M. 2.77±0.77 ng/ml in respect to HFpEF (mean±S.E.M. 7.72±0.76 ng/ml). Moreover, a significant inverse correlation between irisin and LAG values in HFpEF was found (r² = 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 were 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 HFrEF.

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Liraglutide prevented the deposition of Collagen in the animal model of Bleomycin-induced lung fibrosis
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Pathophysiology of idiopathic 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 its 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. Liraglutide was injected into 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 subcutaneously, 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 fluid for analysis of soluble collagen. The mRNA expression of Collagen type I 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, incrients play an important role in the regulation of the synthesis and activity of key enzymes in the formation of collagen fibres and deposition. Since, incrients may be useful molecules in the treatment and prevention of the pulmonary tissue fibrotic processes.

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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, hypertension and ischemic heart disease. It has been suggested that the occurrence 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 chromosome. We assessed age, treatment with GH, pubertal development, lipid profile, diabetes mellitus, body mass index, blood pressure and cardiac and valvular abnormalities. The association between variables was evaluated using Fischer’s exact test and paired samples 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, monosomy 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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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? Louis O’Dea1, James MacDougall2, Andres Digenio3, Brant Hubbard1, Marcello Arca1, Patrick Moriarty3, John Kastelein4, Eric Bruckert5 & Joseph Witzum6, 1AcesaTherapeutics™, Inc., Cambridge, Massachusetts, USA; 2BioBridges, Wellsley, Massachusets, USA; 3La Sapienze University of Rome, Rome, Italy; 4University of Kansas Medical Center, Kansas City, Missouri, USA; 5Academic Medical Center (AMC), University of Amsterdam, Amsterdam, The Netherlands; 6ICAN, Paris, France; 1University of California, San Diego, California, USA.

Introduction
Differentialiation 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) and NPV is Pr(Predicted-Non-FCS = True-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, BML, and history of pancreatitis) and 93.5% with a 5-variable set (apoB/LDL-C, BMI, and history of pancreatitis) and 93.5% with a 5-variable set.

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 ≥ 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/m². 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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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 investigating 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 diabetes: 62 men (mean age 62.4 ± 12.1 years) and 87 women (mean age 60.3 ± 10.9 years) with CKD (≥ 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 to toe systolic blood pressure to the brachial systolic blood pressure, with both determined using an automatic device.

Results
Overall, the mean age was 62.1 ± 10.0 years, duration of diabetes 13.8 ± 10.5 years, HbA1c 7.9 ± 2.2%, ACR 1.635.2 ± 783.3 mg/gCr, and serum creatinine 1.6 ± 1.1 mg/dL. Mean calculated GFR was 62.8 ± 271.73mL. ABI were 1.05 ± 0.24 (Lt.) and 1.01 ± 0.20 (Lt.). TBI were 0.73 ± 0.31 (Lt.) 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 (p = 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 bioelectrical impedance analysis (BIA) are associated with carotid atherosclerosis in patients 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) ≥ 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 ≥ 8.2 kPa reflects fibrosis, LE ≥ 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 ± 8,7) with 6,02 ± 4,99 years of evolution. 85,1% had metabolic syndrome: 97% BMI ≥ 25 kg/m², 76,6% dyslipidemia, 70,2% high blood pressure, 21,3% OSAS and 17% hyperuricemia. 80,8% had ALT > AST, and 48,9% ALT ≥ 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 ≤ 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 ± 10.2 years, 12 males) and NODAT (n = 31, 49.9 ± 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 ± 2 vs. 7.8 ± 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 ± 1.7% in NODAT and 7.79 ± 1.3% in pre-existing diabetics). Serum creatinine levels at the first year of transplantation (1.29 ± 0.75 vs. 1.48 ± 0.53 mg/dL) and at the last visit (1.67 ± 1.58 vs. 2.14 ± 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 ± 27.2 vs. 56.0 ± 29.7 mL/min/1.73 m², P = 0.021) and at the last visit (61.0 ± 27.7 vs. 42.7 ± 21.2 mL/min/1.73 m², 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 diabetics 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 (ProTM) right after diagnosis in an observational prospective study. It was analysed:

CGMS: mean glucose and standard deviation (S.D.), 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/m² (> 30 kg/m² = 23.1%), weight 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, MOOD 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 = 0.036). 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.

Conclusion

Diabetes mellitus is an independent predictor of mortality in patients admitted with community acquired pneumonia.

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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 0.0045, 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 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 fundoscopy. 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 [59(43%) vs. 16(8.38%), P = 0.01], [triglycerides (1.9 ± 1.51 vs. 1.93 ± 1.7 mmol/l, P = 0.09), 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% ± 2.04 vs. 9.2 ± 1.94%, 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.

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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
Historically prospectively collected data of patients hospitalized between January 2011 and December 2013. Patients.

Patients
Patients ≥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 ± s.d., 68 ± 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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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/m²) 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 mg/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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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 measured 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 PM1.5 and SO2 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 PM2.5 and SO2 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 SO2.

Conclusions
It was concluded that higher pre- and post-pregnancy exposures to PM2.5 and SO2 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 were pre-pregnancy BMI of 27.2 kg/m2, age 24–28 years and 25.1 ± 4.8 kg/m2 respectively. Women with GDM were older (mean age 32.5 ± 5 vs. 28.3 ± 5, P < 0.001) and heavier (mean BMI 27.2 ± 5.1 kg/m2 vs. 24.7 ± 4.7 kg/m2, 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 gestational diabetes mellitus were independent predictors of developing GDM (P < 0.05 for all). Low risk women (age < 25y, BMI < 25 kg/m2, 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 Cushings’ 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 Cushings 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 (assessed 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. Acrumegaly 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 n-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

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very limited. Therefore, we investigated the association between gluca-

tion to insulin ratio (GI 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/m², respectively). Participants were assessed for serum fasting and

postprandial GI ratio and divided into tertiles. NAFLD was defined as

ultrasonographically detected fatty liver. Results: The patients in the lowest

tertile of fasting GI ratio had higher BMI, visceral and subcutaneous fat

thickness (VFT, SFT), and HOMA-IR. In addition, postprandial GI ratio was positively

related to the parameters of cardiovascular autonomic regulation. However, there are conflicting data on the impact of hyper- and hypoglycaemia on

cardiovascular autonomic regulation. Further investigation in the inflammatory-apoptotic pathway

and low-grade systemic inflammation may have a role in this process as it is extrapolated by the positive

correlation of FasL concentration and the magnitude of inflammatory response

between AD and type 2 diabetes mellitus (T2DM) while neuronal apoptosis may also be involved in the inflammatory process. Peripheral cytokine levels of IL-1ß, 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-1ß (nIL-1ß), 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 T1DM, T2DM, 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 lowest in diabetes controlled 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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**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 ~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 ± 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 2.3±0.2 g respectively, P<0.05). GF bread 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, z=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 intervene 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 database) 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/m². They were 44 (0.46%) and 41 (0.15%) 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 5.28 (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, hyperlipidemia, 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 multiprotective Symbiotor (symbiotic association of 14–24 strains of Bifidobacterium Lactobacillus, Propionibacterium, Lactococcus lactis, Streptococcus, Acetobacter acetii) and hepatoprotector Glutargin (argnine 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 multiprotective Symbiotor (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 multiprotective Symbiotor 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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Glargine U300 leads to an improvement in metabolic control in 24 weeks with T1DP. The change of the treatment to the new long acting analogues degludec or Conclusions daily dose) 6 m/kg: 0.67 as effective as conventional care at improving glycemia in patients with type 2 diabetes. was better in the telemonitoring and telemedicine than in the conventional group. 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 glycaemia in patients with type 2 diabetes without serious adverse effects.

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Telemonitoring and Telemedicine for Type 2 Diabetes Care: Multi-center Randomized Controlled Trial Jae-Han Jeon¹, In-Kyu Lee¹ & J-Yun Jeong²

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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 = 112), 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% ± 1.03% vs −0.66% ± 1.09% vs −0.81% ± 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 glycaemia in patients with type 2 diabetes without serious adverse effects.

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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 Marta Elena Domínguez-López, Rosario Valíaje, Virginia Morillas, Natalia Colomo, Mercedes Guerrero, Gema Rojo & Marisol Ruiz de Adana Navas Endocrinology Department, Hospital Regional Universitario, Málaga, Spain.

Background There aren’t published randomized studies comparing the clinical impact of degludec and Glargina U300 in the treatment of type 1 diabetes patients. (T1DP)

Objective To compare efficacy and safety of the new long acting analogues Glargina U 300 and Degludec in 300 Type1 diabetes patients treated with basal/bolus treatment.(B&B)

Material and methods Randomized control study 1.1 in 300 T1DP treated with BBT with glarginaU100 or Detemir who change to GlargineU300 or Degludec at 1500 h during 24 weeks, with telemedical visit (using Emminens platform) 6 weeks after the change of the treatment. The efficacy is mainly measured by change of HbA1c, secundary 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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Comparison of insulin degludec with Insulin glargin 300 units/ml in insulin-naive patients with type 2 diabetes mellitus Tomislav Bozek¹, Ines Bilic Curcic² & Lea Siniric Duvnjak²

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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 less percentage of hypoglycemia and 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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Long term results and determinants of outcomes in primary health care diabetes prevention. The DE-PLAN project Aleksandra Gils-Januszewskaja¹, Jaunta Lindström², Noël C Barengo³ & Jaakko Tuomilehto⁴,⁵,⁶

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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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hypoglycemia. Optimal insulin therapy should therefore minimize the risk of hypoglycemia while improving glycemic control. Newer insulin preparations degludec and glargine 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-naïve 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 glargine 300 units/ml, both with metformin. At randomisation, eligible participants discontinued all OADs (DPP-IV inhibitors, sulfonylurea, pioglitazone) with the exception of metformin. Degludec and glargine 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 glycaemia, DPP-IV inhibitors or repaglidiene 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/m², mean baseline A1c 9.5 ± 1.4%) that were randomized (degludec 92, glargine 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 or 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 glargin 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: classical 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 autobody, 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/m² in T1DM and 26.07 kg/m² 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 years) 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 hyperglycaemia. 21 (%42) patients developed steroid induced overt hyperglycaemia compatible with DM and 39 (%78) developed hyperglycaemia 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's 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 outpatient to detect the best time for measurement. We showed that the highest values were postprandial 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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Introduction

The pathogenesis of type 2 diabetes includes an imbalance in free fatty acids, lipids, glucose, and insulin resistance. Malondialdehyde (MDA) is a product of lipid peroxidation which is widely used as an index of free radical damage. Our aim was to assess the effect of aerobic exercise training on serum MDA level and quality of life in type 2 diabetes.

Methods

One hundred and thirty-three middle-aged type 2 diabetes patients were randomly assigned to two groups (exercise, n = 67; control, n = 66). The exercise group underwent 6 months of supervised, aerobic exercise training (3 days/week, 60 min/session). Serum MDA level was measured before and after the training period. In addition, quality of life was assessed using the Turkish version of the 36-Item Short Form Health Survey (SF-36). Data were analyzed with paired t tests.

Results

There were no significant differences between the two groups in terms of age, sex, body mass index, duration of diabetes, or blood pressure. After aerobic exercise training, the serum MDA level was significantly decreased (P < 0.001). The quality of life scores were significantly improved in all domains of the SF-36 (P < 0.001).

Conclusions

Aerobic exercise training can improve the quality of life and decrease serum MDA level in type 2 diabetes patients. Further studies are needed to confirm these findings.

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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 on 64 patients diagnosed with Type 2 DM for at least 6 months, without any microvascular/macrovacular 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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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 SPSSv22 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/m² and with Bypass of $-13.55±5.3$ kg/m², 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 $-0.85±0.90$% and with Bypass a medium of $-1.50±1.66$%. Bypass showed a more significant reduction in insulinemia ($P = 0.001$) and HbA1c ($P = 0.003$). 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 ischemic 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. 0.9) 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 subcutaneous 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 mg/dl (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 estimating low-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 low-density 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), 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 underestimation 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 higher risk subjects such as hypertriglyceridemia and hypo-HDL cholesterolemia. 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, AIC 9.07 ± 2.3%) 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), euagycemia (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 euagycemia. Plasma PAI-1 activity were significantly different during hypoglycemia as compared with euagycemia (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 reaction (VMRr = (S2–S1)/S1) were measured with transon- dulx duplex sonography in 41 patients (age 28.9±6.2 years, duration of DM1 15±4 years, HbA1c 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<200 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 m² was noted in 6 patients, in 15 patients with GFR ≥60 ml/min per 1.73 m². 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 m² compared with the group of patients with GFR ≥60 ml/min per 1.73 m² (P = 0.008) (U-test). S after compression was higher in patients with macroalbuminuria compared with normoalbuminuria (P = 0.0199 (P-test). There was not statistically significant difference depending on HbA1c 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 m²), 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 of the other calcium in the cytoplasm. Hypoxic condition induces endoplasmic reticulum (ER) stress, increase both insulin signaling and insulin resistance. By exposing hypoxia, CaBP-9K KO mice showed more increased level of ER stress marker protein than wild type mice. To examine the cumulative effect on 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 delayed regulation of serum glucose after glucose administration. Serum insulin of CaBP-9K KO mice were decreased compare to wildtype mice. In addition, the insulin 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 1 diabetes to type 2 diabetes.

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GP108
The effect of GLP-1 agonist treatment on serum betatrophin levels and comparison with insulin 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 insulin 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 6th 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 insulin treated group (P = 0.017). There were no significant relation between betatrophin and c-peptide 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 betatrophin 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 senile chorio-retinopathy 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 ßENaC which were the target gene of the MR. We treated MIO-M1 cells with aldosterone. Aldosterone induces a significant up-regulation of MR, ßENaC 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 (< 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 (4 h: P < 0.001, 12 h: P < 0.01) but ßENaC mRNA did not change. We did not find the decrease in ßENaC mRNA. 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 hepatopositis
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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 hepatopositis 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 hepatopositis 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 hepatopositis 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 oxides 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 intragastically 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, glucidaze (Servier, France), the second generation sulfonlurea 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...
in vitro Diazoxide pretreatment of isolated human islets improves pancreatic islet survival and leads to improved islet graft function in diabetic mice. 

**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 sorted 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 pancreatic 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±7.20, 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/m²) 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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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 mU/l and 28.2 mU/l. More importantly, 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 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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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 mU/l and 28.2 mU/l. More importantly, 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 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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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


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.


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 neoplasms.

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 glycermic 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 lamin 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 lipoatrophies. 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/m2 (weight 6 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 lipodytrophsy 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 creatinine level 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 $\alpha$-type laminopathy and the multigenerational family seen in our patient. Multigenerational 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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**Objective**

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 heterogeneous. 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 ketosoadisis 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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**Objective**

To describe the clinical presentation and metabolic profiles of affected family members with GCK c.295T>C (p.Trp99Arg) mutation.

**Background**

Familial Hyperinsulinaemic hypoglycaemia (FHIH) 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. FHIH has been correlated with mono-gene mutations in approximately 48% of cases. Clinical manifestation may vary even in the same affected GCK mutation family.

**Introduction**

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 children, grandson). A father of three children, age 54 (birth weight 3800 g, current BMI-25.9); diagnosed at the age of 20 years. Symptoms of hypoglycaemia (HS) present from postnatal period, with an increased intensity in early childhood. Learning and behavioural problems during childhood. Hypoglycaemia 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 4000 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/after the meal, no relation with 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.

**DO**: 10.1530/endoabs.56.GP125

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**GP126**

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

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**Objective**

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 acromegaloïd-like appearance in patients with LCG, however no case of SBS and acromegaly has been reported.

**Background**

Clinical case 63-year-old man appeared 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 turgescence. 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, LDL-1: 41 mg/dl, triglycerides: 440 mg/dl); increased IGF-1: 269; HOMA-IR: 11.93, A1c:6.4%. 1st OGTT: Impaired glucose tolerance (0 h:101; 2 h:180 mg/dl) and GH-0.5: nadir 0.12; nadir 0.19 ng/ml; second OGTT 10 months after diabetes (glucose 0 h:120; 2 h:204 mg/dl) and GH-0.5: nadir 0.64 mg/dl. 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 other digestive endoscopy were normal. A 17 cm hepatomegaly without steatosis was detected on abdominal ultrasound. Left ventricular hypertrophy was observed in the ECG. In the pituitary MRI was found an area of hypocapasia contrast product with rounded aspect in right half of pituitary gland, passing...
midline to opposite side and prophyseing 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. DOI: 10.1530/endoabs.56.GP126

**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 premeno-pausal 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 HSD17B1 expression in endometriotic epithelial (12Z) and stromal (22B) cell lines. Low-dose of SKA Progestrone and low-dose of SKA-II.10 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 Progestrone and IL-10 may represent an opportunity for the development of new therapies in the clinical management of endometriosis.

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**GP128**

Low-dose SKA Progestrone 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 Progestrone (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-Progestrone and SKA-II.10 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 Progestrone and MPA and the modulation of IL1β protein levels and NF-kB p65 nuclear levels by WB analysis after low-dose SKA-Progestrone, low-dose SKA-II.10, low-dose SKA-Progestrone and low-dose SKA-II.10 (combined treatment), MPA. Low-dose SKA Progestrone was effective in the inhibition of HSD17B1 expression in endometriotic epithelial (12Z) and stromal (22B) cell lines. Low-dose of SKA Progestrone and low-dose of SKA-II.10 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 Progestrone 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/m², 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 (AUCGLP-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 ΔAUCGLP-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 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/CG 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 immunobiochemistry. GLC were cultured and treated with LH or FSH with or without pre treatment with Dyno-4a, a dynamin inhibitor, and cAMP assay performed.

Results
Gene and protein expression of LH/CG 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 Dyno4a, which inhibits dynamin dependent receptor internalisation, inhibited both LH 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/CG 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 CT 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 9 (c.1444C > T, p.Arg482Trp) in LMNA gene, and the final diagnosis of Dunnigan 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 (mSSD) from R-R intervals, spectral power densities (LF: low frequency and HF: high frequency) and spontaneous baroreflex sensitivity (BRS). Both mSSD 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 (mSSD: 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 mSSD (for PCOS: B = −0.108, 95%CI: −0.207 to −0.008, P = 0.033 and for BMI: B = −0.206, 95%CI: −0.303 to −0.020,
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 bioavailable fractions. We performed seventeen-hours circadian salivary androgens analysis and serum steroids circadian profile in 9 classic PCOS (oligomenorrhea + hirsutism/high testosteronemia + 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=0.043) and waist circumference (P=0.011). Both baseline levels and circulating hormones daily exposure were higher in PCOS: testosterone (P=0.001; AUCg=2849.3), androstenedione (P=0.006; AUCg=11327.3), DHEA (P=0.013; AUCg=100.4) and displayed higher BMI (P=0.018; 3314.9 AUCg) compared to controls. PCOS showed higher estrone (P=0.002; AUCg=1700) and 17OHpregnolone (P=0.001) levels compared to controls. No differences were found for serum cortisol, cortisone, corticosterone, 11-deoxycorticosterone, progesterone, estradiol and dehydroepiandrosterone. 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; AUCg=2849.3), androstenedione (69.6 ± 18.7 vs 162.3 ± 49.9 pg/ml, P<0.001; AUCg=2849.3), DHEA (169.2 ± 100.4 vs 349.1 ± 152.1 pg/ml, P<0.001; AUCg=100.4) and 17OHpregnolone (P=0.018) and displayed higher BMI (P=0.011; 3314.9 AUCg) compared to controls. PCOS subjects displayed high serum testosterone, androstenedione, DHEA, 17OHprogesterone, 17OHpregnolone 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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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 pathogenic 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 48,570 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 classified as aggressive (invasive or ki67 ≥3%) or non-aggressive (non-invasive and ki67 <3%). Methylation was associated with a decrease in the expression of only one TSG studied whose expression correlated negatively with the aggressiveness of PAs although only in the SCT subtype (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 CADMI in the pituitary tumours derived from Tpit lineage, a subset of 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 (REMMAH) database. Tumours were classified as aggressive (invasive or ki67≥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, CADMI, CASP8, MGMT and RASSF1. The expression of CADMI was significant lower in SCT and in CT than in SGT (P=0.018 and P<0.001, respectively). Moreover, the expression of CADMI was also lower in CT than in ST (P<0.001). The expression of RASSF7 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 CADMI 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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Introduction
Silent corticotroph tumours (SCT) are a pituitary tumour (PT) subtype of corticotroph lineage that do not clinically express Cushing disease. Immunohistochemical (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 = 0.005) 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, 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 neuroendocrine 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 CTKs 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 (~1% vs control; P < 0.01). Dinaciclib (100 nM) significantly reduced viability in both NCI-H720 (~3% vs control; P < 0.01) and NCI-H727 cells (~62% vs control; P < 0.01). Dinaciclib potentiated the inhibitory effects 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 potentiated Chloroquine effects on LC3B reduction 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.

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 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 GnRH neurons, 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 naive 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 63/93.7%, 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, ZG = 0.49.2 (P = 0.62). 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, ZG = 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-1 and ULN were: 1.57 (0.35–10.00) ng/ml; 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 a dimensional step-wise regression, pituitary microadenoma, IGF-1 ULN 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 = 0.00104), 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 hyponatremia. 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 MCF14 rescues 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 subjects. 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 (NG) 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/m²) 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 compared to the case population, in which the percentage of 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 Fish test (P=0.0159). Several genes tested positive are known to be involved in the reward system and in the hedonic hunger (FTG, OPRM1, GHR1 and LEPR), but we discovered new loci with a novel possible involvement in hedonic hunger. To date, our study is the first NG 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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Hyponatremia-associated mortality and volemia in patients on parenteral nutrition: a prospective multicenter study

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Introduction

In patients receiving Parenteral Nutrition (PN), hyponatremia is associated with increased in-hospital mortality. Our objective was to evaluate the influence of volemic classification (hyponatremia, 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<0.096). 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 were also registered. Stats: univariate and multivariate logistic regression.

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 euvolemia.

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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 hyperglycemia 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 x-ketoglutarate affect the activity of SirTuin histone deacetylases, Jmpd 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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Cerebral blood flow may decrease during very high intensity exercise, completers could reflect an management capacity, throughout multiple mediators The HPA-axis hyperactivity may decrease BDNF production via IL-6 presented lower values of BDNF in relation to the athletes of intermediate group race IL-6 was directly correlated with ... inversely correlated with skeletal muscle mass (kg) (r = -0.469, P < 0.001). Post-race IL-6 was directly correlated with Δ% urea acid (r = 0.341, P < 0.001), Δ% insulin (r = 0.287, P < 0.05), Δ% HOMA-IR (r = 0.289, P < 0.05), Δ% HOMA-B (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% urea acid (r = 0.439, P < 0.001), 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 athletes 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, consuming 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

Sex hormone-binding globulin is more than a sex steroid carrier: A New therapeutic target against obesity and non-alcoholic fatty liver disease Cristina Saez-Lopez, Cristina Hernandez, Rafael Simo & David M Selva Diabetes and Metabolism Research Unit, Vall Hebron Institut de Recerca (VHIR), Universitat Autonoma de Barcelona and CIBERDEM (ISCIII), Barcelona, Spain.

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, consisting of overexpressing human BDNF transgenic mouse with C57BL/Ka-db/db mouse, a diet-induced NAFLD model (by feeding human SHBG transgenic mice and their wild-type littermates with high fructose diet (HFD)) during 8 weeks and a diet-induced obesity model by feeding human BDNF 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. 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 syndrome prediction

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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/DX/ECT in abdominal fat assessment, especially imaging pre-peritoneal, omental and retroperitoneal fat. Our aim was to validate a new 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% premenopause), mean BMI 31 kg/m2 (19.2% normal weight, 28.8% overweight, 52.2% Obesity), came for conventional abdominal US. Thickness of 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 E1; Supersonic and deep subcutaneous fat; Pre-peritoneal fat; Peri-aortic (omentum) fat; Hepatic steatosis area (cm2) and hepatic US noise (dB) (visceral fat); Pre-re nal fat (Left and Right) (retroperitoneal fat). We also obtain: Waist circumference (WC, Glucose, insulinemia, 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-re nal, 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 > 35.4 mm in F (AUC = 0.761; P < 0.001; 74% sensitivity and 60% specificity) and > 35.6 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 viscer al fat, US highlights the clinical importance of strict peri-aortic (omentum) 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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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 hyperinsulinaemic-euglycaemic 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 ± 6.48 to 31.29 ± 2.91 kg/m²) and increase in ISI (4.39 ± 1.95 to 13.68 ± 3.36 mg/kgFFM per min per µU/ml-100). Plasma BCAA in morbid 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-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 312.19 ± 54.88 µM; insulin clamp BCAA 352.47 ± 88.77 to 211.56 ± 44.16 µM) following bariatric surgery but also without any changes in short-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. DOI: 10.1530/endoabs.56.GP151

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.

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 (NCI, Ferrer inCode) based on 6 genetic predisposition risk scores (GPs). Each GP consists of several SNPs which were shown to be implicated in

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, erythrocytes CD235a, endothelial cells CD144) and exosomal marker CD9 correlated with FABP4, interferon γ, adiponectin, FABP4, TNNc, inhibiton γ-expressing EVs at 6 months’ follow-up (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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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% during follow-up was seen in patients with previous mental disorders.

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%) 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/m², 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 glycemia, 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 3.99 ± 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 < 0.005) 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 ± 73.15 vs 159.4 ± 43.75, P < 0.005 and 592 ± 187.03 vs 487 ± 171.01, P < 0.005, respectively), Prevotellaceae diminished but not significantly (20.92 ± 30.09 vs 13.02 ± 21.69), and odoribacteraceae increased (16.63 ± 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 steatohepatitis

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In this study, new mental disorders in the form of eating and substance-related disorders were higher than in general population (1.8% versus 1%) 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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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 intraperitonentially 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.

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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 patterns 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: RNU11, RNU2, RBM22, SRSF3; down-regulation: RNU1). 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. RNU11, U2AF1, PRPF40A, PRPF8, RBM22, RNU6atuc, 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 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.

GP158
Dietary intake of visceral 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 validated 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 (β = 0.334, P = 0.024) in the total population. The miR-143 expression in visceral adiposity among morbid obese was negatively associated with non-hydrogenated vegetable oils (β = 0.317, P = 0.036), and directly associated with butter (β = 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 (β = 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 morbibly obese and non-obese participants.

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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 adipocyte function 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-exposure. 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 administration of CL-316243 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 ACACB were upregulated in Cold whilst IL18R1, TLR4 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 NERP3, IL13 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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**GP160**

Physiological regulation of brown adipose tissue in obesity by mild-cold exposure, a β3-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 weaning 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 PPARG, mtTOR 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 ACACB were upregulated in Cold whilst IL18R1, TLR4 and EMR1 were downregulated. Similarly, β3 increased FASN whilst downregulating IL18R1, IL6 and STAT3. Finaly, Exercise upregulated FASN, SCD1, HK, ACACA, ACACB and PDK2 whilst downregulating NERP3, IL13 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 of energy expenditure (EE) warm and EEcold; EEcold; EEwarm. CIT was measured by indirect calorimetry during warm conditions. In the present study, we investigated the effect of seasonal temperature variation on CIT in human adults.

Results
CIT was inversely associated with the average maximum outdoor temperature during the week (R²=0.1737, P<0.0001) and the month (R²=0.1424, P=0.0031) before the visit date. EEbasal and EEcold were not significantly related to outdoor temperatures, EEbasal R²=0.0074, P=0.4218 (TempMax7d), R²=0.0168, P=0.2252 (TempMax30d) and EEcold R²=0.0132, P=0.2840 (TempMax7d), R²=0.0035, P=0.5831 (TempMax30d). The difference between
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**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 (E2), 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 E2, 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 E2, T and TSH for each of the development stages, i.e., the newborn, 14-days, 28-days, 42-days and 3-months stages) infants, positively associated with E2/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 -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 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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**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 attended 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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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 ages, 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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Early AR is a risk factor for PCOS and high BMI later in life, thus, children with PCOS with normal/late AR. Early AR was not associated with serum testosterone timing of AR associated with PCOS-diagnosis independently from BMI.

5.60 years, PCOS had lower birth weight (3406 vs. 3507 g, levels at menarche, 14, 31 and/or 46 years were analyzed. Findings: Women with PCOS had higher 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.

Materials and methods
In this prospective, population-based longitudinal Northern Finland Birth Cohort 1986 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.

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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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 circulating 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 during the 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 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/mm². Results showed no difference (P ≥ 0.05) 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, IRS-2, PKC and receptors showed similar expression in T-females (P ≥ 0.05) compared to that of C-females, while, on the contrary, the Akt and GLUT4 RNAm was lower in T-females (P ≤ 0.05). Interestingly, IRS-2 transcript showed a tendency to a higher expression (P ≥ 0.05) in T-females, while, on the contrary, the Akt and GLUT4 RNAm was lower in T-females (P ≤ 0.05). Results suggest that prenatal and postnatal exposure to T affects the insulin signaling on beta cells during postpubertal development and induced a dual effect in adipose tissue at the transcriptional and morphological levels.

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GP166

Endemic goiter and breasts diseases in adolescent girls
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Research indicates the relationship between breast and thyroid gland. Breast tissue contains the highest concentrations of iodine, so shortfall 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 clinical signs and postnatal exposure to T affects the insulin signaling on beta cells during 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 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/mm². Results showed no difference (P ≥ 0.05) 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, IRS-2, PKC and receptors showed similar expression in T-females (P ≥ 0.05) compared to that of C-females, while, on the contrary, the Akt and GLUT4 RNAm was lower in T-females (P ≤ 0.05). Interestingly, IRS-2 transcript showed a tendency to a higher expression (P ≥ 0.05) in T-females, while, on the contrary, the Akt and GLUT4 RNAm was lower in T-females (P ≤ 0.05). Results suggest that prenatal and postnatal exposure to T affects the insulin signaling on beta cells during postpubertal 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 (puberital 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 test levels of E2, testosterone, FSH and LH. Direct clinical interview and standardized tests were carried out: low self-esteem, social phobia, emotional instability, suicidal ideation, suicide attempts and self-harm.

The results were compared with those obtained in a population subjected to stress due to sexual orientation (cissenders): ‘homosexuals, lesbians and bisexuals’ (LGBT) 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 LGTB 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 psychomorbidity in the group with IG 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 psychomorbidities 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 placental tissue of clinically healthy women, as well as its relationship with alterations in birth weight.

Methods
Placent 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 β 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 risks 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 mechanism is not 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, <5.5 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 glycemia (mean fasting and postprandial glycaemia) and food intake (amount of carbohydrates, proteins, fat and calories) 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 = -0.379, 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, coelic acid, 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/m², P > 0.05). TS girls presented lower IgG concentration, CD4% and lower CD4/CD8 ratio compared 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 PZ was the lowest (P < 0.001).

**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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**GP172**

**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 Fisher) 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-7c (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 specificity of the result on a bigger sample of patients.

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**GP173**

**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. Parathyroid glands 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 not the very important first research results. 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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**GP174**

**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), i.e., 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 (uc) 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 2 twice daily injections, superior to once daily, and continuous SC infusion normalizes serum calcium (sc), serum phosphate (sp), and uc. Ascendis Pharma is developing TransCon PTH, an inductive prodrug of PTH(1-34) for the treatment of HP. In its prodrug form, PTH(1-34) is transitory 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, spA, 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 ≥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.

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


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Hypoparathyroidism is a rare disorder characterised by hypocalcaemia and analysis of a long-term, open-label, single-centre study. Maintenance of key biochemical parameters with recombinant human (rhPTH1-84, Natpar) 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 ≥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, 53%) 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, 3–34) 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.

**GP177**

**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 unetectable parathyroid hormone (PTH). Recombinant human

**GP178**

**The global, prospective, observational PARADIGM 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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**PARADIGM**, 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 ≥900 patients, including ≥300 receiving rhPTH(1-84). Follow-up data collection on each patient is planned for ≥10 years. Patients with a diagnosis of HPT of ≥6 months are eligible for inclusion; exclusions include inability to provide informed consent, enrollment 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/m² 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 rhPTH1-84 in a clinical trial setting (ie, data capture was prior to US Food and Drug Administration approval). Data from PARADIGM will provide physicians with needed information on the natural history of HPT in patients prescribed conventional treatment and in those prescribed rhPTH1-84.

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GP179
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 βCaOx > 4 and βHPO > 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 (βCaOx) and calcium hydrogen phosphate or brushite (βHPO4). The group included 81 females and 21 males, mean age 55 ± 15 years. In 93 (91%) patients, stones 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 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 βCaOx and PTH (P=0.029, r=0.25) and between βHPO4 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 (rhPTH1-84) 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 homeostasis 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. rhPTH1-84 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 48.19±7.8 years; 81.6% female); 40 patients (81.6%) completed 60 months (Mean ±SD, 72.2±20.5 months). rhPTH1-84 was 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] mmol²/l; BL, 3.4[0.51] mmol²/l). 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 homeostasis.

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GP181
Is there HIV-associated hypoparathyroidism?
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Background
Parathyroid hormone (PTH) secretion in response to hypocalcaemia 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 (48–54) years. In 406 patients, albumin concentration was available and in 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).

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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; conversely, 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 96.4% of patients, 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 regimens on clinical manifestations of hypoPT patients should be more intensively investigated.

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Pituitary/Growth Hormone & IGF Axis

Adrenal insufficiency induced by anti-PD1/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

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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-renal 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 T3-G 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 11β-hydroxylase enzyme, blocking the final step of cortisol synthesis in adrenal cortex. Daily dosage ranges from 250 to 6,000 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 2750 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 high morbidity

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Background

The 2017 World Health Organization classification of pituitary tumors established that, pituitocytoma, 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-functional 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 pituitocytomas, 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 severe hyponatremia (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

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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) was performed for worsening of diabetes. The treatment was then commenced with interferon α2b and 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 μg 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 α2b, 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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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 the height and IGF-1 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-1 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 (Biomarkers in Personalized Medicine, Medical University Graz) were analysed to identify putative differences between IGF1R-aAbs positive and negative volunteers. 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 = 0.012)), 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-aAbs 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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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 ectopic lipid content in newly diagnosed patients with acromegaly before and >6 months after successful surgical or medical treatment.

Patients and Methods: 21 patients with acromegaly underwent a hypersulminulinemic, eucluglycemic glucose clamp (HEC), dual x-ray absorptiometry (DXA) scan, and MR spectroscopy to quantify lipid content in liver (HIL) and muscle (IMCL).

Results: 10 patients were controlled by surgery alone and 11 patients were controlled by a somatostatin analog (SA). Mean ± s.e. serum IGF-1 levels (μg/l) before and after treatment were 696 ± 90 and 221 ± 33 with no treatment-specific difference either before (P = 0.75) or after treatment (P = 0.11). Insulin sensitivity assessed by mean ± 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 ± 0.4 (before) vs. 4.7 ± 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). HIL (% CH2O/water) increased after disease control, regardless of modality: 21.4 ± 0.8 (before) vs. 67.2 ± 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 HIL 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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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 apparent signs 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 μg/dl); 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 suppression test (DST): 17.56 μg/dl, 2 day 2 mg DST: 13.2 μg/dl.The high levels of ACTH (8.52 and 8.41 μg/ml), insufficient increase serum cortisol and ACTH levels post CRH-stimulating testing and no mass on pituitary 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/ml) and plasma ACTH (401 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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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 multi-farious endocrine adversities of checkpoint inhibitors.

Case 1: 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 hypoechogenic goiter with increased vascularity.

Case 2: Patient 2 is a 76-year-old male with metastatic melanoma with rapidly declining to suppressed TSH levels, fT4 ×3 ULN and fT3 ×2ULN after the second infusion of nivolumab. He had a palpable hypoechogenic 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.

Case 4: 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 hypoechogenic ‘honeycomb’ gland. His TSH reached a peak of 1.0 ng/ml, fT4 <0.3 ng/dl) and fT3 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.
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 gonadals 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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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.
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 8a, a deubiquitinase that rescues proteins involved in the regulation of ACTH synthesis in corticotroph cells. In the present study we tested the antisercreatory and antiproliferative efficacy of a commercially available specific USP8 inhibitor (IC50 3.1 µM USP8; >90 µM USP7) in immortalized murine corticotroph tumour AIT-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 transcription 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±21 respectively), 9 out of 11 cases at the 1 µM (% suppression 34±15), and 7 out of 11 at the 0.1 µM (% suppression 24±16). No toxicity was observed in any of these concentrations. In AIT-20 cells the USP8 inhibitor (1 µM) decreased cell number (% suppression 35±2) 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 0 out of 11 to µM treatment (% 30±24). Co-treatment with EGF, an ACTH secretagogue whose receptor is the best characterized target of USP8, in EGF-overexpressing AIT-20 cells shifted the antiproliferative and antisercreatory response to the USP8 inhibitor (% suppression 36±3 vs 27±2 and 64±7 vs 57±7 at 1 µM respectively), indicating that in part the effect of USP8 inhibition is mediated via its inhibitory crosstalk with the EGFRe 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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GP199
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 8a, a deubiquitinase that rescues proteins involved in the regulation of ACTH synthesis in corticotroph cells. In the present study we tested the antisercreatory and antiproliferative efficacy of a commercially available specific USP8 inhibitor (IC50 3.1 µM USP8; >90 µM USP7) in immortalized murine corticotroph tumour AIT-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 transcription 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±21 respectively), 9 out of 11 cases at the 1 µM (% suppression 34±15), and 7 out of 11 at the 0.1 µM (% 24±16). No toxicity was observed in any of these concentrations. In AIT-20 cells the USP8 inhibitor (1 µM) decreased cell number (% suppression 35±2) 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 0 out of 11 to µM treatment (% 30±24). Co-treatment with EGF, an ACTH secretagogue whose receptor is the best characterized target of USP8, in EGF-overexpressing AIT-20 cells shifted the antiproliferative and antisercreatory response to the USP8 inhibitor (% suppression 36±3 vs 27±2 and 64±7 vs 57±7 at 1 µM respectively), indicating that in part the effect of USP8 inhibition is mediated via its inhibitory crosstalk with the EGFRe 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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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 paragangliomas 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 MEG3 (an imprinting gene, 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) and methylation status (using bisulfit modification and methylation specific PCR). These analyses revealed that MAX and MEG3 were substantially expressed in the different tumor types, and distinct 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.

DOI: 10.1530/endoabs.56.GP199

GP200
Pharmacological characterization of somatostatin receptor subtype 3 as a potential strategy to treat non-functioning pituitary adenomas
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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-

GP201
Epigenetic and post-transcriptional regulation of the SSTR5 gene in somatotropinomas
Sergio Pedraza-Arevalo1,2,3,4, Alejandro Ibáñez-Costa1,2,3,4, M Carmen Vázquez-Borrego2,3,4, Miguel Branco3, M Ángeles Gálvez-Moreno2, Alfonso Soto-Moreno2, María A Korbonits8, Manuel D Gahete1,2,3,4, Mario Chiralambous2,5, Raúl M Luque1,2,3,4 & José P Castañó1,2,3,4,5
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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 situ 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 be involved in the expression regulation of SSTR5, whereas no significant differences were found in the expression of the SSTR5-AS1.

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
In patients 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 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.

DOI: 10.1530/endoabs.56.GP203

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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Background
Cushing’s disease is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma, resulting in glucocorticoid excess. First-choice treatment is transphenoidal pituitary surgery, using either a microsurgical or endoscopic technique. Convincing evidence supporting the choice for one of both techniques, either based on treatment results or complication rate, is lacking. Objectives
We aimed to compare endoscopic and microscopic transphenoidal 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 transphenoidal 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 microsurgically 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 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 7.0%).

Conclusions
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.

DOI: 10.1530/endoabs.56.GP204
Long-acting pasireotide reduced urinary free cortisol (UFC) in most patients with Cushing’s disease (CD) during a 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 1.5–5×ULN 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 = 0.01). 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**

<table>
<thead>
<tr>
<th>Surgical status</th>
<th>n</th>
<th>Response rate, % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior surgery</td>
<td>27</td>
<td>40.7 (22.4–61.2)</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>123</td>
<td>41.5 (32.7–50.7)</td>
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</table>

<table>
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<tr>
<th>Sex</th>
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<tbody>
<tr>
<td>Male</td>
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<td>40.6 (23.7–59.4)</td>
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<tr>
<td>Female</td>
<td>118</td>
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</table>

<table>
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<th>Age quartile (range, years)</th>
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<th>Response rate, % (95%CI)</th>
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<tr>
<td>Q1 (18–27)</td>
<td>31</td>
<td>32.3 (16.7–51.4)</td>
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<tr>
<td>Q2 (28–36)</td>
<td>42</td>
<td>40.5 (25.6–56.7)</td>
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<tr>
<td>Q3 (37–46)</td>
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<td>50.0 (33.4–66.6)</td>
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<tr>
<td>Q4 (48–71)</td>
<td>39</td>
<td>41.0 (25.6–57.9)</td>
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</table>

<table>
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<th>mUFC quartile (range, nmol/24 h)</th>
<th>n</th>
<th>Response rate, % (95%CI)</th>
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<tr>
<td>Q1 (44.7–272.5)</td>
<td>37</td>
<td>54.1 (36.9–70.5)</td>
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<tr>
<td>Q2 (277.6–392.5)</td>
<td>38</td>
<td>47.4 (31.0–64.2)</td>
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<tr>
<td>Q3 (400.8–603.9)</td>
<td>37</td>
<td>32.4 (18.0–49.8)</td>
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<tr>
<td>Q4 (603.7–1670.0)</td>
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<td>31.6 (17.5–48.7)</td>
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<table>
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<tr>
<th>Adenoma size*</th>
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<th>Response rate, % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microadenoma</td>
<td>68</td>
<td>35.3 (24.1–47.8)</td>
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<tr>
<td>Macroadenoma</td>
<td>49</td>
<td>49.0 (34.4–63.7)</td>
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<tr>
<td>Non-visible</td>
<td>29</td>
<td>44.8 (26.4–64.3)</td>
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</table>

<table>
<thead>
<tr>
<th>Maximum tumour diameter quartile (range, mm)</th>
<th>n</th>
<th>Response rate, % (95%CI)</th>
</tr>
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<tr>
<td>Q1 (3–5)</td>
<td>22</td>
<td>36.4 (17.2–59.3)</td>
</tr>
<tr>
<td>Q2 (6–8)</td>
<td>35</td>
<td>42.9 (26.3–60.6)</td>
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<tr>
<td>Q3 (9–11)</td>
<td>27</td>
<td>29.8 (13.8–50.2)</td>
</tr>
<tr>
<td>Q4 (12–54)</td>
<td>33</td>
<td>51.5 (33.5–69.2)</td>
</tr>
</tbody>
</table>

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

**DOIs**

**GP205**

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

**GP206**

Clinicopathological correlations in pituitary thyrotroph tumors from a cohort of 23 patients
The thyrotroph tumors or pituitary neuroendocrine tumors (PiNET) 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 (SSTR2A, SSTR5), 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 plurihormonal 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 clinical and biological signs of acromegaly. Three TSH monohormonal tumors were positive for TSH and PRL. Only 3 patients with GH co-expression presented positive for both TSH and GH. Two tumors expressed TSH, PRL and GH and 4, 8, and 12 weeks after CC. Erectile function and hypogonadism symptoms were evaluated 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 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 CC therapy. Recovery of gonadal function by clomiphene was independent of PRL levels.

DOI: 10.1530/endoabs.56.GP208

**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 hypophysitis. 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 pituitary samples (CP) from autopsies and organ donors. The genes (SSTR2, SSTR5, DRD2 long and short isoforms, AIP, CDH1, Kiss1, Arrb1, Arrb2, Ghr, Ghrh, Elk10, Plagl1 and Pebp1) were measured by RT-qPCR using TaqMan technology and the levels were normalized by three reference genes (β-MRPL19, TBP and PGK1).

Results DA, 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 r=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 r=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.

DOI: 10.1530/endoabs.56.GP207

**GP208**

The role of clomiphene citrate in the resolution of hypogonadism in male patients with prolactinomas under cabergoline therapy

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Division of Endocrinology, Hospital das Clínicas, Federal University of Pernambuco, Recife, Brazil.

Background Dopamine agonists (DA) are the treatment of choice of prolactinomas. Cabergoline is preferable to bromocriptine due to its greater effectiveness and better tolerability. 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 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 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 CC 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 1290 to 221,000 mU/l (median 198,000 mU/l; normal 30–545 mU/l). Decrease of prolactin occurred in 114 (94%) patients; prolactin level was normalized during treatment in 49% of cases; 96/121 (81%) patients had significant adenoma shrinkage; 77/99 (78%) patients with pre-treatment visual abnormalities had visual improvement, 67/71 (94%) - 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 enonadal 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 stereotoxic 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. ± 10.6) years old with a mean age at transplant of 35.2 (s.d. ± 10.3) years old. 11.3% of the patients tested (n=48) 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 hypo- gonadism. 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). Toremilimumab (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. Hyponatremia was defined as a Serum Na level (SNa) < 135 mmol/l. A positive response to therapy was defined as reaching SNa > 135 mmol/l (eunatraemia) following 72 hours of treatment. Urine osmolality-UOsm > 500 mos/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 mos/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 < 1 liter/24 h. 26/47 (55.3%) patients had UOsm > 500 mos/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 at least one criterion predicting a lack of response to 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% (CI: 0.23–8.26%) 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 perfluorooctanoic 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 a FAK-phosphomimetic mutant p-FAK-Y407E (constitutively active) by converting amino acid residue Tyr-407 to Glu-407 was able to reverse the PFOS-induced Sertoli cell injury through proper organization of actin microfilaments and microtubule (MT) organization across the Sertoli cell cytosol, making these cytoskeletons 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 reverse 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 p53, involving Akt1/2 (a family of serine/threonine kinase) downstream in a more recent study in rodents, overexpression of a constitutive active phospho-mimetic mutant of p-Akt1/2-T308E (such as p-Akt1/2-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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Coxackievirus 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 a 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 bioinformatic 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−/− testes 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 1) affect the downstream effects on junction disruption and actin reorganization via structural protein at the BTB, CXADR functions as a crucial signaling mediator to 2) 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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CHI is a genetic syndrome that combines reductive 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 CHI.

Introduction
CHI is a genetic syndrome that combines reductive and brain abnormalities.

Methods
A series of 56 adult patients (48 males, 8 females) presenting with CHI 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.7312_7314delP.Arg2405del, class 3), KISSR (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 I 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.10257T>A, p.Leu3425S). 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%. CHI 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 CHI and CM1. Multicenter studies and systematic brain MRI may be required to extend the phenotype and the genotype of CHI 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 that in 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 analytic 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, testosteron and 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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Primary ovarian insufficiency (POI) is a highly heterogeneous condition defined by the occurrence of amenorrhea, hypoestrogenism and hypergonadotropism 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 chromosomeal 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 epicanthus 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 HEK 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 compared to FOXL2-WT- and FOXL2-p.Y186* cells. On this regard, it is widely recognized that mitochondrial dysfunction is involved in the development of several diseases, namely PD, AD, and T2D. We hypothesized that the novel FOXL2-p.E92* 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* variant would eventually determine the onset of POI in the BPES-affected patients.

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GP221

Mitochondrial phenotype of FOXL2 variants associated with Blepharophimosis, Ptosis and Epicanthus Inversus Syndrome (BPES)
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GP222

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 choriongonadotropin (hCG) and fetal LH-functioning. It is the so-called “LHCGRex6A”, truncated, intracellular receptor isomorf produced by alternative cryptic exon stop-codons located between the 6th-7th out of 11 exons. Its function is unknown, although pseudohyphenrodactyli and 46-XY female-like phenotype were associated with LH/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-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. Equicont, 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 = 0.05; n = 6), reflecting the qualitatively different LH/hCG-specific signal. While no different b-h LH- and hCG-induced progesterone response was found, 24-h hormone production were about 2-fold higher upon hCG than LH exposure of siRNA-treated hGLC (hCG-LH = 35.7 ± 5.5 ng/ml; progesterone-hCG = 64.0 ± 11.3, basa = 24.2 ± 3.2, means ± s.e.m.; Mann-Whitney’s; P = 0.05; n = 6). 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 should be investigated in the not-readily available primate male tests cells, providing wider picture of LH/hCG co-evolution.

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GP223

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 also is 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 was 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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**GP22**

### 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 transpersons 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 1;10) and total body fat decreased with 25% (95% CI 1;29). Changes in lipids per s.d. change in VAT were 0.2 mmol/l (95% CI 1;30) in total cholesterol, 0.1 mmol/l (95% CI 0;12) in LDL, 0.0 mmol/l (95% CI 0;02) in HDL, and 0.0 mmol/l (95% CI 0;00) in triglycerides. In transmen (median age: 24 years, IQR 21–33), VAT increased with 6 grams (range ~31–179 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 1;6). Changes in lipids per s.d. change in VAT were 0.1 mmol/l (95% CI 0;10) in total cholesterol, 0.0 mmol/l (95% CI 0;10) in LDL, 0.0 mmol/l (95% CI 0;10) in HDL, and 0.1 mmol/l (95% CI 0;02) 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<sup>fl<sup>ox</sup>/Nestin<sup>Cre</sup>) or in cells that express the leptin receptor (GHR<sup>fl<sup>ox</sup>/LepRC<sup>Cre</sup>). These females were mated and, when the first day of gestation was identified via the identification of the copulatory plug, they were individually housed and further studied.

**Results**

Pregnant GHR<sup>fl<sup>ox</sup>/Nestin<sup>Cre</sup> 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<sup>fl<sup>ox</sup>/LepRC<sup>Cre</sup> 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 77% (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<0.002 and P<0.001). Serum TSH was higher in patients with 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.

**Conclusions**

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. DOI: 10.1530/endoabs.56.GP224

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 (FNMC) represents 3–9% of thyroid cancer cases. Although the susceptibility genes for syndromic FNMC are known, most cases of FNMC are nonsyndromic and the genetic causes are unknown.

Patients and methods
We conducted a multicenter study to identify a candidate susceptibility gene for nonsyndromic FNMC. We collected blood specimens, clinical and pathological data from 38 kindreds with FNMC (32 with two affected members, six with ≥2 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 ≥ three cases of FNMC in each kindred. We filtered and identified the germline SNPs and INDELS using Haploype 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 <0.01, we identified two novel germline heterozygous mutations in kinesin family member1B gene (KIF1B1) in two kindreds. In the first family, five of five affected members presented a mutation c.2680G>T (p.T827I) mutation in exon 23. We believe that the remaining member could be a photocopy 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).

Conclusions
We identified two families with FNMC 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 FNMC.

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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 withdrawal 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 radiosine treatment compared with that before RAI treatment (6307±1527/μl vs 5476±1439/μl, 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 CRP 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 histopathologic entity. Nowadays there are controversial publications about its aggressiveness 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 between 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 (21.2%) 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% surgicals 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 IVb. 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% received also a lateral neck lymphadenectomy. 55 (98.21%) received radioactive iodine remnant ablation. More than 1 RAI were applied in 9 (21.2%) patients. Median radioactive activity received was 105 (100–118) mCi. After a median follow-up of 4 (1–8) years, excellent response was observed in 86.4%, indetermined response (biochemical or structural) 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 aggressive 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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GP230
Peptide receptor radioiodide 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 177Lu-octreotide (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 111In-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 111In-DTPA-octreotide scan (grade ≥3; more than liver) and a clear somatostatin receptor type 2a (SSTR2a) expression on tumor by immunohistochemistry. Retrospective evaluation of historical 111In-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 177Lu-octreotide was only effective in the patients that had the combination of high uptake on 111In-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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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 scoring thyroid nodules. TI-RADS 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
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 (47.2%) ≥2.5 cm. None of the malignant nodules in TR3 were ≥2.5 cm. Negative correlation (r = -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 TRS 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 = -0.304, P = 0.04) was found between size and malignancy.

Conclusions
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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GP231
Related recurrence factors in a Spanish cohort of differentiated thyroid carcinoma. Cadit-CAM Study
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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 4.67 (95% CI 1.15–18); TG-Ab 4.86 (2.4–9.9); positive lymph nodes 4.38 (2.7–9.2), 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 (0.48–1); lymphadenectomy 0.8 (0.5–1.28) and histology 0.7 (0.34–1.4). Recurrence treatments were: iodine-131 (50%); 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: 28% alive without evidence of disease, 24% alive with structural disease, 27% undeterminate or biologically 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 extension, 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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**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 BRAFV600E 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 BRAFV600E 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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**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, cabozantinib, vandetanib and sunatenib were analyzed. In a pooled cohort of 922 patients with advanced MTC, metastases in lymph nodes were 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 MRT/ 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 be used in the future.

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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 cholecystokinin-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-(DG阝)-Ala-Tyr-Gly-Tip-Nleu-Asp-PheNE2) 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 1.5 and 3.7 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 an 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 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. The relationship between treatment response (excellent, indeterminate, biochemically incomplete, structurally incomplete) or final status of the disease (remission, persistent disease, death) and BMI was evaluated. 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.

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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 (2.0×10^6 cells/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 mm³, CM-Dil 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 transwell 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 helpfull 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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Comparison in survival of the seventh and eighth editions of the American Joint Commission 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 DTC 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.

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 the general population.

Our preliminary conclusions may be redefined after performing thyroid diagnostics in more women carrying CHEK2 gene mutations.

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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 H157T 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
Aloka, Albatroz, Alboccet, Albacete, Spain, 62 women, aged 25-60 years (average 42.5 years), with 1100delC, IVS2+1G>A and del5395 mutations of CHEK2 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 1100 delC. 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 7 based 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 the general population.

Our preliminary conclusions may be redefined after performing thyroid diagnostics in more women carrying CHEK2 gene mutations.

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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 benign in category IV.

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**GP240**

Orthotopic PDX Mouse Model of human primary 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 (bTH) 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-IRESpmCherry. A patient-derived ATC primary culture grown in bTH 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, p16, p14ARF, p27, p21, TP53, TP73, TP63, TP62 were mutated in all ATC tumors.

**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 IncRNAs 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 (hypoechogenic pattern, irregular margins, microcalcifications, etc.) and cytopathology TIR3B, TIR4 or TIR5 according to 2014-SIAPE 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 IncRNAs (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 IncRNAs 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 IncRNAs (MALAT1, NEAT1, HOTAIR, H19, PVTT1, 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 preAmpl 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 IncRNAs 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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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.

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 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 Chi-square and Student’s T-tests.

Results

All patients were followed for a minimum of 3 years postoperatively (146±3.92 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=0.9) 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±15.8 and 52±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 ≤ 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-free status was evaluated after initial therapy and at last follow-up.

Results

Sixty-six patients were studied: 54 (81.8%) girls, age 14.5±2.0 months, 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 radioactive iodine. 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 (sPTG). Interestingly, the sPTG cutoff of 37.8 ng/mL displayed 81% sensitivity and 100% specificity to predict excellent response.

Conclusion
DRS after initial therapy and sPTG 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 isoflavone genistein 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 function 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 iodosyronines 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 contrast, 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/m²) 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 mechanisms(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, Tye, free triiodothyronine (T3), free thyroxine (T4), 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 Tye even Phe/Tye ratio were normal associated with FT3, FT4 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 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).

<table>
<thead>
<tr>
<th>Group</th>
<th>T4</th>
<th>TSH</th>
<th>RRR</th>
<th>95% Conf Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>Normal</td>
<td>Normal</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>Low</td>
<td>Low</td>
<td>3.8</td>
<td>0.021</td>
<td>(1.2–11.7)</td>
</tr>
<tr>
<td>G2</td>
<td>Low</td>
<td>Normal</td>
<td>2.1</td>
<td>0.031</td>
<td>(1.1–4.2)</td>
</tr>
<tr>
<td>G3</td>
<td>High</td>
<td>Low</td>
<td>2.1</td>
<td>0.002</td>
<td>(1.3–3.3)</td>
</tr>
<tr>
<td>G4</td>
<td>Normal</td>
<td>Low</td>
<td>1.2</td>
<td>0.314</td>
<td>(0.8–1.89)</td>
</tr>
<tr>
<td>G5</td>
<td>Normal</td>
<td>High</td>
<td>1.4</td>
<td>0.018</td>
<td>(1.1–1.9)</td>
</tr>
<tr>
<td>G6</td>
<td>High</td>
<td>Low</td>
<td>0.9</td>
<td>0.849</td>
<td>(0.4–1.9)</td>
</tr>
<tr>
<td>G7</td>
<td>High</td>
<td>Normal</td>
<td>1.7</td>
<td>0.040</td>
<td>(1.02–2.8)</td>
</tr>
<tr>
<td>G8</td>
<td>High</td>
<td>High</td>
<td>3.7</td>
<td>0.001</td>
<td>(1.7–7.7)</td>
</tr>
</tbody>
</table>

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 ($P=0.0014$). 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 analyzed the histological and functional phenotypes of the mice which has thyroid specific mitochondrial dysfunction by targeting Crf1 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 encycotic 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 thyroxine 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. TH, 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 mg/Kg) 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 PEPT1 content 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 hyperthyroidism 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-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 mice 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 Methimazole 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, CDSL, was highly T3-dependent in liver, spleen and bone. CDSL 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 thymimetic 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-MRM and data analysis was performed using MascQuant 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 ≤ 0.05, fold change ≥ |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 targeted 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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**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 cytokine production and proliferation was assessed. The potential gene target was identified and validated.

**Results**

The increased expression of miR-4443 induced CD4+ T cells dysfunction by targeting TRAF4, which may cause Graves’ diseases.

**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? A retrospective study in a single tertiary care hospital

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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 assess 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 has 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 (0.98–2.58) 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 = 0.044). 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 normal reference 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 considered if ATPO was $\geq 35$ U/ml (Immulite 2,000). The cut-off for subclinical gestational hypothyroidism (HSG) was TSH $\geq 3.72$ 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 $<2500$ g.

The quantitative 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 67.8% children with weight $<2500$ g 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 m/g/day (0.95 mg/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 nor 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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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

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. Neoplasms 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 (Pembeolizumab 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 hyperthyroidism 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 hyperthyroidism, however substitutive Levothyroxine was initiated when hyperthyroidism was found. At the end of the follow-up 64.7% continued on Levothyroxine, although 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 hyperthyroidism and the rest with hyperthyroidism 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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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.

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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 described 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, levothyrroxine, or immuno-suppressive 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 ± 8.7% vs 6.2 ± 10.1%, P = 0.331), 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-RT 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 immune 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 = 9) had lung cancer, followed by melanoma (19.4% (n = 14), bladder 11.1% (n = 6), kidney 9.3% (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 15.4% 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 ICPI 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 (DIIT) study, 8044 participants were included from 2004–2005, 2010–2011, 2015–2016 and 2018, representing around 20% of the Danish population. The participants were screened for thyroid function, thyroid auto-antibody positivity, and non-thyroidal autoimmune disease. 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.

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% of TPOAb- and TgAb-positive patients developed hypothyroidism and 18.7% developed persistent subclinical hyperthyroidism. The median onset was 5 weeks for hyperthyroidism and 9 weeks for hypothyroidism.
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 hyperthyroidism, and 4.5% reported hypothyroidism. 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 hyperthyroidism, 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 non-thyroidal 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 = 0.016). 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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Thyroid Cancer -Benign Thyroid Disease/Treatment

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 months (P = 0.001), 12 months (P = 0.005) and 24 months (P < 0.001). At 24 months, the rate of responders (subjects with euthyroidism 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 euthyroidism 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.

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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**GP269**

Tailored thyroxine treatment and gastric acid output in humans

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Hypothyroid patients with thyroid 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 (r² = 0.1209; P < 0.0223) and the diminished H+ concentration (r² = 0.1275; P = 0.0219). A multivariate analysis revealed that pH act as an independent variable in determining the dose of T4 (P < 0.0229). 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 = 13%). 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 enlightened 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 bioimpedance 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-Altmann 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-Dunnet; 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 severe hirsutism and virilization due to 3β-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 adenoma pain, vomiting and hypertension. She was born with Ambiguous genitalia and operated at age 8 years. She has severe hirsutism, with score of 18 and virilization. There is 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, Endocrinology data showed height DHEA-S and urinary 17 K S 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-hydroxyprogrenolone and DHEA concentrations in response to ACTH. 17-hydroxyprogrenolone 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-hydroxyprogrenolone 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 1.5 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
Forty-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 K (2011–2017), with arterial hypertension, adrenal glands lesion according to 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, adenorectomy 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 asthma, 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 adenarche at the age of 12 (well developed pubic, 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/m². He possessed coarse hair all over his body including auxiliary, pubic and chest area. Geminal examination revealed Microphalous (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 ng/ml). Estradiol (E2): 24.2 pg/ml (N: 15–50), 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: 4000 ng/dl (N: 3.5–5.1), karyotype analysis showed 46.XX. Abdominal pelvic US was 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 hostocortin 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 hypercortisolism 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/m². 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, 83.33% 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 hypercortisolism of PCS is caused by the increased activity of the CRH neuron which stimulates the production and release of ACTH.

Discussion

The fact that some symptoms are more specific to CS than PCS, the activity of the CRH neuron which stimulates the production and release of ACTH, overproduction of cortisol. The hypercortisolism of PCS is caused by the increased activity of the CRH neuron which stimulates the production and release of ACTH.

Discussion

The fact that some symptoms are more specific to CS than PCS, the activity of the CRH neuron which stimulates the production and release of ACTH, overproduction of cortisol. The hypercortisolism of PCS is caused by the increased activity of the CRH neuron which stimulates the production and release of ACTH.

Discussion

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Discussion

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Discussion

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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 hypergonadonal 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 three-weekly maintenance HD on the same device (Gambro AK200 Ultra S) in Zemun Clinical Hospital. CAH hypergonadonal 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 shown in Table.

Discussion
Our results demonstrated the regular male age-related LH/T levels in control examinees with no significant change after HD sessions. T level at D0 (either normal or low) is significantly less than previous T (D0), 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 hypergonadonal 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 Cushing’s syndrome at age 30 years old. She had undergone resection of craniopharyngioma at 10 years old and repeated removal of desmoid tumors. Polypsis was observed in the stomach, duodenum, upper jejunum, and large intestine. Polypstomacy 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/m2). 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

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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, while hypoglycemia is rare. An unusual case of a septic patient with hypokalemia and hypoglycemia 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, hyperkalemia and hyponatremia 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 hyponatremia and the associated nephrogenic diabetes insipidus, persisted and were both restored only after correction of serum magnesium.

Conclusion

Flucanazole 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 hyponatremia and hyponatremia. 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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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 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.

Observations

The highest incidence was in sixth decade (34.21%). Regarding the tumour localisation, 60.53% were found in the left adrenal gland, 34.21% were visualized 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 hadphaeochromocytomas, 2 were

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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, bruisings and insomnia during the last four months. In addition, polyuria and polydipsia 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
- Adrenaline: 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 hypochronic left adrenal mass on an abdominal magnetic resonance. After surgery adrenocortical carcinoma with areas of necrosis and hemorrhage is confirmed. It exceeded adrenal gland and reached peripancreatic tissues. It presented perineural invasion but no vascular invasion. Negative hemorrhage is confirmed. It exceeded adrenal gland and reached peripancreatic tissues. It presented perineural invasion but no vascular invasion. Negative hemorrhage is confirmed.

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.

Objectives
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).

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 postoperative 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 undiagnosed. Hereby we present the case of a normotensive 50-year old female patient who was diagnosed of probable left
Adrenal insufficiency during prednisolone treatment in patients with polymyalgia rheumatica or giant cell arthritis – 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 oestrogeen treatment free for 2-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 supplemental 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%, CI95%: 7.4–28%) had adrenal insufficiency. Current prednisolone dose correlated negatively with 30 min P-cortisol (~32 mmol/L/mg prednisolone, CI95%: 9.5–55 mmol/L/mg, P=0.0086).

Conclusion
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.

P20
Prevalence 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 159 mmHg 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). Evaluation of PA was based on the combination of vasalsartan, 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/LμU/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 doses, which ranged from 50 to 200 mg (mean 104.5 mg). At the last follow-up 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 (9.2±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 suppressed 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 12x6.6 mm hypoechogenic 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 μg/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 mmHg. 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 undergo right adrenalectomy. The postoperative 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 oncocyes which are large and polygonal cells with eosinophilic cytoplasm because of abnormal accumulation of mitochondria. 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 mm lesion was detected. Right -side adrenalectomy was applied to the patient. The histopathological diagnosis was reported by the Pathology Department as oncocyadic 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 adrenocytic neoplasm on imaging. Diagnosis is made histopathologically, so adrenalectomy is the mainstay of therapy and laparoscopy is now the most diffusive approach. According to Weiss criteria: the presence of one major 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 response during the stress reaction. The study aimed to describe the differences of steroid response between hypoglycaemia 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 hypoglycaemia, 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 accordance 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 between 1.9-9 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 method
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 ≤ 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 ± 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 ± 2.11 cm, 1–8.2 cm) than those on right side (2.11 ± 0.96 cm, 0.6–5.5 cm). From 174 non-functioning AI, 58.6% (113) presented NP and 34.5% (61) PACS. Comorbidities: 58% (101) hypertension, 32.2% (56) diabetes, 33.9% (59) dyslipidemia and 31% (54) obesity. Mean BMI: 30.1 ± 7.4 kg/m². 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 hypercortisolism: 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 concentration over the course of two days. Blood samples were drawn in 3-hour intervals. A cardiological 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 ± 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 ± 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 system may deliver a new therapy option in avoiding increased levels of IL-6 in AI patients.

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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% 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_001105247.1), 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 hastily?

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Introduction
Isolated corticotropin insufficiency of hypophysis with consequent 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 1-24ACTH. 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 1mg 1-24ACTH stimulation (proper deoxycorticisol concentration >18 µg/dl) then the Metryrapone 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 1-24ACTH, the 1mcg 1-24ACTH stimulation (proper cortisol concentration >18 µg/dl) then the Metryrapone tests were performed. 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 criteria but had a negative SLT, the lowest potassium level was 3.4 on several occasions (without other contributory factors), with baseline aldosterone concentration (PAC) insufficient deoxycorticosterol increase after Metryrapone 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 1-24 ACTH can give false negative and positive results and should be followed by low dose 1-24ACTH test and Metryrapone 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 to 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%) 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 concentration 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 benefited 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 pg/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 lobe of right adrenal gland and a mass measuring 22×25 mm in the lateral lobe 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 heterogeneity and necrotic components after contrast. Thorax CT showed sequelae findings 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 antibacterial 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 may represent one explanation for the good performances of CT scan in the SPARTACUS study. We propose that AVS aldosterone values be normalized on cortisol-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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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.

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 = 0.25. The patient showed poor tolerance of anti-aldosterone treatment and eventually underwent right adrenalectomy, resulting in normalization of BP and remission of PA. Immunohistochemical 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.

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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 90' and 1 at 120'. 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.

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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 erroneous 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 treatment. Images were acquired at 24, 48 h, and late images, off of DXM, on 5th/7th day.

Results

20 (55.6%) 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 result was glandular asymmetry (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 pressure resolved 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 mg/ml/h) did correlate to INCS positivity (P = 0.001) and adrenalectomy (P = 0.045), however neither plasmatic aldosterone nor aldosterone/renin ratio > 50 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 was 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 aldosteronism 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 renal 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 an important leukocytosis and thrombocytopenia. Gram staining of cerebrosinal fluid pointed out gram-negative diplococcie and latex agglutination testing was positive for type B meningococcial 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, meningococccaeamia, infant.

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P36

Hypoadosteronism induced by trimethoprim: hyponatremia is frequent

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Introduction

Hypoadosteronism is characterized by the development of hyperkalemia, but can also induce hypovolemic hyponatremia. Trimethoprim can cause hypoadosteronism through mineralocorticoid resistance. That hypoadosteronism can induce hyponatremia in absence of Addison’s disease has been questioned. We studied the electrolyte disturbances found following initiation of trimethoprim therapy.

Material and methods

Retrospective, analytical. Laboratory tests of 100 consecutive patients receiving trimethoprim 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 trimethoprim. 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 67%: 0.92 (0.6) (< P < 0.0001). 35% patients developed hyperkalemia. 10%: SK >5.5. BSK was higher in patients developing hyperkalemia: 4.32 (0.38), 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: 159.6 (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). 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 trimethoprim-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

Trimethoprim-induced hypoadosteronism is frequent, potentially causing hyperkalemia and, more often in our series, hyponatremia. In patients presenting both, creatinine levels rose, suggesting hypovolemia onset. Trimethoprim, 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 electrolyte disturbances should not be attributed to Addison’s Disease.

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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/m² (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).

Discussion

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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P40
Cardiovascular risk in patient with incidentally detected adrenal masses – associated with metabolic syndrome and hypercorticism
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Background
Adrenal incidentalomas (AI) represent incidentally discovered adrenal masses, without symptoms 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 occurrence 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 these 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 Framingham 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 agressive 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 no-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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P42
The response of C19 Δ5-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 11β-hydroxylated dehydroepiandrosterone 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 (NCAH), is the milder form of the 21-hydroxylase deficiency, with the estimated incidence of 1:1000 worldwide.

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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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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 PAI, 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 significantly higher 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/m²) 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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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 (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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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 or 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 adrenomas (aldosterone-producing adenoma n=27, corticotropin-producing adrenal adenoma n=8 and pheochromocytoma n=5) and non-functioning adenomas in combination with arterial hypertension (n=19).

The RAAS (angiotensin II, angiotensinogen, renin) of plasma and serum is measured in peripheral blood by Enzyme Immunoassay, and aldosterone is determined in 24-hour urine by Enzyme Immunoassay.
P47
The renin-angiotensin-aldosterone 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-aldosterone 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±2.8 kg/m²; mean blood pressure 140/83 mmHg) and eight matched healthy volunteers (female n=5; male n=3; age 52±21; BMI 25.2±4.3 kg/m²; 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=0.002), angiotensin-1-7 (P=0.03) and angiotensin-1-5 (P=0.03), as well as in a reduction in aldosterone-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 pittitary 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 supravacunous 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 nmol/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 incidenta-lomas. 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 g/dl, and was confirmed by levels ≥3 g/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 findins.

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, 7.14 vs 44.9%, P=0.08), diabetes (OR 1.4, 36 vs 25.6%, P=0.4), osteoporosis (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/24h, P=0.5), DHEAS (70.2 vs 46.2 µg/dl, P=0.1), ACTH (20.1 vs 18.2 µg/ml, P=0.7) or bilaterality (OR 1.4, 20 vs 15%, P=0.7). No difference was 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.

DOI: 10.1530/endoabs.56.P50

P50 Is the adrenal vein sampling the gold standard diagnostic test for the subtyping of primary aldosteronism?

Antonio Garcia & Angel Molino

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 infusion 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 mass index was 30.81 (21.4–47.80). 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 (10.3%). After follow up, 20% of patients were completely cured (normotensive without 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 Cushings’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-sctigraphy, 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 (88%) 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%) chemoreduction. 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 adrenocortical cancer 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 hypercortisolism 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-oophorectomy 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 mmEq/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 G68 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 hypotension, 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 potassium infusion need were not suspended. Bilateral adrenalectomy was performed. He died due to pulmonary embolism 2 months after adrenalectomy.

Conclusion
Common treatment 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 and cell death (necrosis and apoptosis) were determined by WST-1 assays or flow cytometry following induction with cumate.

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 adenoma
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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: 65.3 ± 11.3 years; NF: 64.03 ± 11.0 years; P > 0.560), body mass index (pACS: 27.71 ± 5.5 kg/m²; NF: 27.8 ± 4.2 kg/m²; 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 ± 0.36; 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 (AUROC 0.837 (0.737-0.936); P < 0.0001), showed that a DHEAS ratio of 1.36 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, 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 valproate, levetcetramaz , 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 whether the patient presentation could be a manifestation of Cushing syndrome. in this patient 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 clearance 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 to is 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 before collection. Any sample with blood contamination should be discarded, smoking affect salivary 11beta-hydroxysteroid dehydrogenase type 2, this increases
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 (SalAUCmorning), and the second covering the afternoon and the evening (SalAUCafternoon).

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 SalAUCmorning levels were similar among conv-HC and DR-HC, contrariwise SalAUCafternoon was lower with DR-HC. Morning F was lower in patients than controls: a value <5 nmol/l presented 90% SE and 95% SP in detecting patients (AUC 0.979). Also morning E levels were able to differentiate AI from controls: E <0.45 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 cortisone exposure (SalAUCafternoon) 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 decreased in 24hours, confirming hypoglycaemia.

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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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 licorice. She recently attended an outpatient appointment with a cardiologist and investigations including MRI 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 hirsutism. On examination, she had a BMI of 41 kg/m², 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. FPC-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-insulin 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 hypercortisolism. 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.

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 tests 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 mmol/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 0.598–0.76.3). SP dropped to 60% (95% CI 0.49–0.68) 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 mmol/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 0.66 mmol/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.
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 defined 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 (NCT021161258), 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:
45% 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).

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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P61
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-fluorodeoxyglucose (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. Hemangiomia 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=0.039) 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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P62
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 substitute 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 micro-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 micro-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 cortisol secretion. In the absence of a clear picture of CS adrenalectomy is not indicated. The patient symptoms and comorbidities may be related to excessive cortisol secretion.

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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P64
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 bd, valsartan + hydrochlorothiazide 160/25 mg qd, bisoprolol 2.5 mg qd, atorvastatin 20 mg qd. Irrelevant family history. After right hemiadecectomy 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/m², 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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Introduction
Low S-cortisol levels are often found when assessing patients with clinical symptoms of adrenal insufficiency. However, the frequency of low S-cortisol levels is not well described. We aimed to investigate the prevalence of low S-cortisol levels and to identify indications for testing.
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, 79% (n 227) 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 order to avoid unnecessary concern.

DOI: 10.1530/endoabs.56.P65
P68: Association of the BclI glucocorticoid receptor polymorphism with metabolic parameters in female patients with adrenal incidentaloma
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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 BclI 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 adrenocorticotropic hormone (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 leukocytes. 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 BclI polymorphism had significantly less suppression of cortisol levels after 0.5 mg dexamethasone (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 BclI polymorphism display relative glucocorticoid resistance of the hypothalamo-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 of subclinical cortisol excess.

DOI: 10.1530/endoabs.56.P68

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, Cushing’s syndrome or only small amount of them and sometimes can present signs of hormone excess: virilisation, Cushing’s syndrome or only small amount of them. 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 years.
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 were administered in 39 patients.

Results
Secretory tumors were diagnosed in 23 cases and non-secretory in 26 cases. Twenty second 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-nd or 4-th stage and 12 patients were diagnosed as secreting 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.

DOI: 10.1530/endoabs.56.P69

P70: Adrenocortical carcinoma: retrospective analysis of a series of clinical cases
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¹Department of Endocrinology, La Rabta Hospital, Tunis, Tunisia.

Adrenocortical carcinoma (ACC) is a rare and aggressive tumour. At diagnosis 21% has metastasizes. 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 (ENSA18 2008) is 82%, 61%, 50% and 13% respectively.

Objective
To describe the epidemiological and clinical characteristics, as well as the evolution, treatments and outcomes 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, secretary status neither mitotane therapy in our cohort.

Table 1

<table>
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<th>Stage</th>
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<tr>
<td>II</td>
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<td>1 (5%)</td>
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<td>IV</td>
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<tr>
<td>ENSAT Stage at follow-up</td>
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<tr>
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<td>7 (35%)</td>
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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.

DOI: 10.1530/endoabs.56.P70

P71: Imaging characteristics of pheochromocytoma
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Imaging characteristics of pheochromocytoma

<table>
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<tr>
<th>Table 1</th>
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<td>ENSAT Stage at Diagnosis</td>
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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 (MF) 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 majority of cases to a positive 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 (p.Val84Met) (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 paraffin embedded sample. In our serie, genetic testing was performed on first grade relatives of patients affected, being diagnosed two first grade relatives of PD.

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 second grade relative was carrier of the mutation.

References

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P73

Analysis of a pheochromocytoma case series over 12 years: a specialty hospital experience

Manuel Cayón-Blanco, Virginia Narango-Velasco, Carolina García-Figuera-Mateos, Lourdes García-García-Doncel, Rosa Márquez-Pardo, M. Gloria Baena-Nieto & Francisco Mateo-Vallejo

Hospital SAS Jerez de la Frontera, Jerez de la Frontera, Spain.

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 hemodynamic 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 assessment 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 hypertensive 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 cm (range: 1.5–10 cm).

Preoperative selective alpha-blockade was performed with phenoxybenzamine in 7 cases and 4 patients received non-selective alpha-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.

DOI: 10.1530/endoabs.56.P73

P74

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 pheochromocytoma. This report aims to describe the outcomes of laparoscopic resection for pheochromocytoma 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 alpha and beta blockade. Patients who didn’t meet Rozen’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

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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 volume expanders were documented in 4 and 3 cases, respectively. No arrhythmias were documented. Postoperative results: treatment for transient hypertension was needed in 2 cases, 2 patients suffered from hypovolemia 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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P75

Malignant pheochromocytoma discovered upon consultation for painful erections

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Introduction

Pheochromocytomas (PCCs) and paragangliomas (PGLs) 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 gynecomastia. 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 gland. The patient was hypertensive, normotensive, but have no explanation why it was not the case. The workup of patients with large sporadic pheochromocytoma and very high norepinephrine secretion be normotensive? Yes, they can! Maria Dolores Perez-Ramada1, Isabel Ramos-Gomez1, Paula Fernandez-Trujillo-Comenge2, Ana Delia Santana-Suarez2, Manuel Nistal-Nival-Viñecera3, Agnieszka Kuźni3, Carmen Acosta-Calero1, Claudia Arnas-León1, Sara Quintana-Arroyo & Francisco Javier Martinez-Martín1
1Internal Medicine Department, University Hospital of Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain; 2Endocrinology & Nutrition Department, University Hospital of Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain; 3Endocrinology & Nutrition Department, Hospitales San Roque, Las Palmas de Gran Canaria, Spain; 4Outpatient Hypertension Clinic, University Hospital of Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain.

Results

A 361.5 ng/ml (UNL 100) with 24 h urinary metanephrine 264 g( normal) and normetanephrine 6 g/24 h, with mild hypotensive symptoms. 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 adrenalectomy, having started treatment with doxazosin 4 mg bid followed by bisoprolol 10 mg bid, adequate hydration and CINa 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 pheochromocytomas need the same preparation (including adrenergic blockade, hydration and salt supplementation) although it might elicit symptomatic hypotension.

DOI: 10.1530/endoabs.56.P76

P76

Can patients with a large sporadic pheochromocytoma and very high norepinephrine secretion be normotensive? Yes, they can!


Introduction

This work was designed to determine the incidence of normotensive pheochromocytoma in a population of sporadic cases. The incidence of normotensive pheochromocytoma in our population.

Methods

Patients with large sporadic pheochromocytomas follow the Endocrinology department of the Mohammed VI University Hospital of Marrakech between 2012 and 2017.

Results

Among the 23 cases of pheochromocytomas followed in the endocrinology department of the Mohammed VI University Hospital of Marrakech between 2012 and 2017.

Conclusions

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 pheochromocytomas need the same preparation (including adrenergic blockade, hydration and salt supplementation) although it might elicit symptomatic hypotension.

DOI: 10.1530/endoabs.56.P76

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.

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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. Neurofibromatosis develops in 0.1–5.7% of NF1 patients and pheochromocytoma 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 neurofibromatoma after alpha-adrenergic blockade. Following surgery, the patient had normalized the blood pressure and had achieved a moderate hypertension.

Conclusions
This case illustrates the importance of the etiologic diagnosis and treatment in the management of secondary hypertension. The patient was relentless progressing to end-stage renal failure but presently her blood pressure is well controlled while minimally treated, and her renal function has markedly improved.

DOI: 10.1530/endoabs.56.P79
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; 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 Phenoxbybenzamine 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 Phenoxbybenzamine 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 (γ=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.

DOI: 10.1530/endoabs.56.P81

Cardiovascular Endocrinology and Lipid Metabolism

P83
Arterial hypertension from the adrenal gland: Prognosis and predictive factors of recovery after chhirurgical 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 arterial 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 phaeochromocytoma (group 2) and 11 patients with Cushing’s syndrome (group 3)). Adrenalectomy was performed in all patients. 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.

Results
After adrenalectomy, a significant decrease in blood pressure <140/90 mmHg without any antihypertensive drugs. Predictors of recovery were determined by calculating Odds Ratios.

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 inflammation 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 adrenomas producing 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, BAAL, VAI, WHR, WHIR). The collected data were statistically analysed using the Statistica 12 (P ≤0.05). In the analyzed group mean concentration of 25-OH vitamin D was 20±8.4 ng/ml, fasting glucose 111.5±29.8 mg/dl, insulin 13.2±9.9 uU/mL, HBA1C% 6.1±0.7, HOMA-IR 3.8±2.9, CRP 2.8±1.1. Insulin concentration correlated positively (P ≤0.05) with BMI (r=0.46), VAI(r=0.21), WHIR (r=0.12), WHIR (r=0.42). CRP was statistically higher (P ≤0.05) in patients with higher BMI (r=0.13), WHIR (r=0.07), WHIR (r=0.10). There was no significant 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, BAAL, WHIR and WHIR) 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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**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 ± 13.6 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/m²) than in PA patients (27.8 ± 1.1 kg/m²), 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 μg/ml vs 29.4 μg/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.

DOI: 10.1530/endoabs.56.P84

**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 arterial adenoma or hyperplasia, in whom primary aldosteronism, hypercortisolism and phaeochromocytoma were appropriately excluded. All patients underwent transcranial 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.

Discussion

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 ± 5.9 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 = 0.04). Also, percentage variation did not show statistical significance in either group.

Conclusion

PA patients showed larger aortic root as compared to 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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**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-OHDI 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 and being followed-up during 33 years.

The patient had normal height, bone health, diabetes and mortality in those patients.

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-OHDI. 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-OHDI. Little is known regarding height, bone health, diabetes and mortality in those patients.

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P88  
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, fatigue, muscular cramps, nausea, anorexia and elevation of blood pressure. 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 statin use in the last days. The laboratory examination 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 pressure. After admission to our hospital, we evaluated nad treated the patient, also prevented a potential acute renal failue from rhabdomyolysis and life-threatening arrythmias, and the diagnosis of Primary Hyperaldosteronism was made.

Keywords: Rhabdomyolysis, hypokalemia, CK, primary hyperaldosteronism.

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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, fatiguability with the impossibility of maintain orthostatism, dispnea and dizziness. Clinical evaluation revealed normal blood pressure, IMC 34.7 kg/m² with pale skin. The paracrine 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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Phaeochromocytomas 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

Conclusion
In patients with spontaneous hemorhoma with no vascular anomaly, pheochromocytoma should be considered. Because of hyperplasia of left adrenal gland and undertaken analysis we decided for wait and watch

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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 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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P92 Severe pheochromocytoma crisis, Type B, resulting in Takotsubo-like cardiomyopathy and fulminating 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 fulminating 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 >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 transesophageal echocardiography revealed a reduction of LVEF to ~15% and a Takotsubo-pattern image of diffuse hypokinesia with apical ballooning. Phenoxbenzamine treatment was initiated immediately. Active haemorrhage or erosion 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 phenoxbenzamine 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 intitation of central VA-ECMO support. Cardiac function was progressively restored and VA-ECMO was removed on day 12, with an LVEF >50%. Treatment with phenoxbenzamine 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 hyperperfusion, 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 Functioning adrenal incidentaloma false positive for 18F-FDG-PET/TAC

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An adrenal incidentaloma > 4 cm in size is considered suspected of malignancy and therefore often sent to the adrenalecctomy 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 cholesangioMRI 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 adenoma. So the patient was sent to laparoscopic cholecystectomy and right adrenalectomy. The morphological and immunophenotypic pathological analysis show a picture of a mixed type adrenal oncocyteoma.

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 oncocyteoma, very rare adrenal tumor usually benign and non-functioning, can be considered in these cases.

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P94 Difficult Management of Autoimmune Polyglandular Syndrome Type 1

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Autoimmune Polyglandular Syndrome Type 1 (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 hypothyroidism (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 mucosal hyperpigmentation and in the abdomen, loss of pressure, but also hypotension and oligoanemia. Laboratory assays revealed hepatocytolysis, hyponatremia (natrium: 118 mmol/l), hyperkalemia, hypoglycemia and hypocapnia (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, normal thyroid stimulating hormone and free thyroxine values under levothyroxine. Follicle stimulating hormone (FSH) concentrations were high (23.4 µU/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 administered and specific melaralorcolitolcoid replacement was required. Hydrocortisone in bolus dose was administrated intravenously, 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 restored. 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 – 15 cm on the right and 11 cm on the left, without invasion of adjacent structures. PET-CT scan showed intense hypermetabolism of the adrenal masses. Bone marrow biopsy and flow cytometry were negative for lympho-proliferative disease. Plasma fractionated free metanephrines were normal, excluding pheochromocytoma. The patient 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 hyperglycemia. 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. DOI: 10.1530/endoabs.56.P94

P96

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/m²). The preoperative examination discovered hyperparathyroidism and an adrenal adenoma. Evaluated in the last Endocrinological Department, was diagnosed also with non-functional pituitary macroadenoma and anterior pituitary insufficiency, two non-functional neuroendocrine pancreatic tumors and Recklinghausen neurofibromatosis. He underwent a minimally 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 anesthetic risk for the next subtotal parathyroidectomy. The pancreatic tumors was nonsecretory and no evolutive signs during 2 years. Family investigation revealed son with primary hyperparathyroidism (operated) and prolactinoma (Cabrigeone), one daughter with primary hyperparathyroidism (operated) and pituitary prolactinoma (Cabrigeone) and one daughter with hyperprolactinaemia. 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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P97

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/entecavir/tricitabine and atazanavir, and had a CD4 levels of 705/mm3 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 tumors, 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 marrow 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 hypermetabolism 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 phaeochromocytoma, 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 exacerbatory primary effusion lymphoma, solid variant, often associated with HHV8 infection, which was also found in our patient. DOI: 10.1530/endoabs.56.P97

P98

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 adenalecetomy 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/m2), enlarged supra-clavicle fat pads, blood pressure of 150/80 mmHg hyperpigmented skin, legs edema. Hormonal profile showed high levels of 17-hydroxypregnenolone (634 mg/dl), normal 5–25 mg/dl, with loss of circadian rhythm, very high GH (free urinary cortisol), of 4728 mg/24 h (normal 20–190 mg/24 h), high ACTH level (619.9 ng/l, normal 7.2–63.3 ng/l), non-suppression at low dose DXM (dexametasone) and 2 day of 8 mg DXM, 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 20–190 mg/24 h), high ACTH level (619.9 ng/l, normal 7.2–63.3 ng/l), non-suppression at low dose DXM (dexametasone) and 2 day of 8 mg DXM, high testosterone level (2.16 ng/ml, normal 0.2–0.75 ng/ml) and very low serum cortisol, 17-OH-Pg, estrogen, testosterone and plasma rennin while on DXM. Hypertension control and correction of the hypokalemia. The patient had a sister who had never had menstrual cycle. Biochemical examination showed severe hypercalcemia and hypokalemia (K 2.7 mmol/l) , metabolic alcalosis (PH 7.496) and basal serum cortisol was very low (0.925 mg/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 ng/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-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-adrenal testes removed in childhood, ambiguous external genitalia, a male karyotype (46XY) and normotensive. Hormonal examination showed a very low serum cortisol, 17-OH-Pg, estrogen, progesterone and plasma rennin while ACTH, FSH, LH, progesterone were increased. Conclusions
17α-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 17α-hydroxylase deficiency might be suspected. DOI: 10.1530/endoabs.56.P100

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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 lumber 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 phaeochromocytoma 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 phaeochromocytoma 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 phaeochromocytoma. Large, bilateral adrenal tumors may cause Addison’s disease, which, if left unrecognized, may also endanger the patient. DOI: 10.1530/endoabs.56.P99

P100

17-α hydroxylase deficiency in an adult female patient with hypertension 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 usually 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 37-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 alkalosis (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 0.1 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-adrenal testes removed in childhood, ambiguous external genitalia, a male karyotype (46XY) and normotensive. Hormonal examination showed a very low serum cortisol, 17-OH-Pg, estrogen, and plasma rennin while ACTH, FSH, LH, progesterone were increased. Conclusions
17-α hydroxylase deficiency is a rare cause 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. DOI: 10.1530/endoabs.56.P100

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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 patient 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 17β-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. Adrenalecetomy 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 c.375G>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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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. I Some of the unusual sites for paragangliomas include the kidney, urethra, urinary bladder, prostate.

Case report
A 27-year-old man presented with severe 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, sweating and palpitation in association with markedly elevated blood pressure (220/100 mmHg). These crises are consistent and severe 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, T2 hyperintense with microcalcification. Adrenal glands were normal and no other lesions were seen on the rest of the body. MIBG shtagraphy 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.

ENDOCRINE ABSTRACTS (2018) VOL 56
Cushing’s syndrome is a disorder characterized by the endogenous hypersecrecion 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, amenorrea, 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 adenaoma measuring 3.2 cm in her left adrenal. The adenaoma was surgically excised. A month later laboratory evaluation revealed low morning cortisol and hydrocortisone was administered. Menses recommended 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 amenorrea, 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 β-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-gestation choriocarcinomas typically arise from gonadal organs but they may originate in extraginal 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/m2. Examination and USS confirmed a right adrenal mass lesion which may be neoplastic. A year later bone biopsy revealed choriocarcinoma. Serum α-fetoprotein and β-hCG levels were normal.

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 hypersecrecion 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, amenorrea, 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 adenaoma measuring 3.2 cm in her left adrenal. The adenaoma was surgically excised. A month later laboratory evaluation revealed low morning cortisol and hydrocortisone was administered. Menses recommended 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 amenorrea, 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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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 complaining of poor hypertension control, sporadic diaphoresis, not significant weight loss. Performed abdominal CT scans revealed multiple large liver lesions both with enlarged regional lymph nodes of suspected metastatic origin. Other CT scans and histopathologic investigations found no primary tumor, except few gastric erosions, diverticulosis coli and benign rectal polypl. On account of the patient’s slight recurrent flushed 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 Tc-99m 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 small 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 Sandostatin LAR, he underwent also 177La Dotata therapy in Oncology Center, Gliwice. The size and number of the liver lesions are under control.

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 emergencies.

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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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Endocrine Abstracts (2018) Vol 56
**P111**

**Effect of 177Lu-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 2015. 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 adrenalectomy with pathological result of large cell neuroendocrine carcinoma (Ki-67 60%). The post-surgical [111In] DTPA-octreotide scintigraphy (Octreoscan) revealed hypercapitant lesions in the pancreatic tail, beginning treatment with lanreotide autogel 120 mg/28 days and sunstitib 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 evololinson (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 nmol/l and serum peptide C 18.7 ng/ml). On 21/07/2017, a first dose (177 mCi) of 177Lu-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 177Lu-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, an 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, 177Lu-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 the adrenal glands were analyzed. The clinical symptoms, the hormonal activity of the adrenal glands were analyzed.

Results

Thirty-two patients (72.7%) had adrenal hypertension, 12 (27.3%) had no hypertension. The group of patients with adrenal hypertension, women predominated - 26 (81.3%) and 6 men (18.7%), mostly of working age (50.5 ± 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 with hypertension was its crisis course, resistance to antihypertensive drugs. The reason for visualization of the adrenal glands in patients with hypertension was its crisis course, resistance to antihypertensive drugs.

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 adrenocorticotestora, in 14.3% by aldosterona.
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 α-blocker intake he underwent surgery. The pathology report revealed ACC. Case 2: A 54-year-old woman, with hypertension and incidentomas 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 16HU. Hormonal activity was excluded and the patient was diagnosed with lipoid 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 lipoid 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 lipoid 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 laterization in adrenal venous sampling. Patient underwent laparoscopic adrenalectomy. The pathology report revealed ACC.

Conclusions

1. 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.

DOI: 10.1530/endoabs.56.P113
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 5 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, 72%). 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 RECIST 1.1 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 600mg). 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 RT2 Profiler PCR Array (Quagen). Fold change (FC) was calculated with the 2ΔΔCt 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 < 0.005). 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 candidate targets 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 CDK4/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.

DOI: 10.1530/endoabs.56.P115

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, 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. 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.

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, outcome in patients at Helsinki University Hospital.

Methods and patients
We included all patients diagnosed with adrenocortical carcinoma (Weiss score ≥ 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 (1–20) 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 this. 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 21 ± 3 (18–45), mean Ki67 17% (1–40%), mean Weiss score 7.1 (4–9) and Helsinki score 4 (4–48). Thirty-three (89%) patients underwent primary surgery, metastases were resected in 4. Thirty (81%) received adjuvant mitotane therapy, 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 ACC and 11.3% in SPheo; NS).

Conclusion
ACC is an aggressive disease and the 5-yr survival rate of 67% was better than in most previous reports. There were no complications in ACC patients compared to 16 complications in ACC patients (P = 0.047). There were no complications in ACC patients compared to 16 complications in ACC patients (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 ACC vs 72.5% in SPheo; NS). ACC were adrenals tumors whereas one ACC was adrenal and abdominal (P = 0.034). The tumor size was significantly lower in ACC than in SPheo (4.0 ± 2.0 cm vs 5.5 ± 2.4 cm; P = 0.047).

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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 ± 17.2 vs 53.6 ± 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 ± 2.0 cm vs 5.5 ± 2.4 cm; P = 0.047).

Discussion
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. Peroperative 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, imagining, 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 ± 14.5 yr; 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

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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 measurements 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 hyperinsulinemia. 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, presence of insulinoma. But an abdominal CT revealed no pancreatic tumor, and 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 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 leviteracetam 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 3.5–6.0) within 28 hours of fasting, high plasma insulin and C-Peptide levels of 13.8 mU/l (3–13) and 2.6 μg/l (1.0–3.1) respectively. Screening for both sulphonylurea hyoglycaemic agents and circulating insulin antibodies was negative. Abdominal MRI and 18FDG-PET 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 EUSRA10 needle (19G, Teawaong). 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 adrenalsvenous sampling prior to adrenalectomy.

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Introduction
Adrenal venous sampling (AVS) is considered the reference standard to select patients with unilateral aldosteronoma 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 incidentailoma. 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=0.091). 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=0.068) 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, catecholamines or aldosterone: 87% for cortisol, 8% for catecholamines 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 being a selection criteria in the majority of the cases. On the other hand cortisol secretion evaluation was the most affordable and accessible measurement in the studied clinical setting; thus it was done in all the subjects. Catecholamines 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. Conclusion. 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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Genetic background as a predictive factor of 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.

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
We 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; SDIH 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 imagalogical characteristics on anatomical (CT or MRI scan) or functional techniques (18F-fluorodeoxyglucose PET/CT scan) or functional techniques (18F-fluorodeoxyglucose PET/CT scan) or functional techniques (18F-fluorodeoxyglucose PET/CT scan).

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 sympathetic 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 treated 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, EGLN1, KIF1B, SDHA, SDHB, SDHA2, 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 SNPEffект.

Results
Germline mutations of Pheo/PGL genes were present in at least 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 (7.6%).

Conclusions
No founder mutation occurred (7.6%). NGS of Pheo/PGL are in accordance with the literature. No founder mutation occurred (7.6%).

P126

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 recognized 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 evaluate 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 screening 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 prevalence 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 misssense) 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 consequence regarding genetic counseling.

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P127

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 controlled 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 mitotane 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 CR and MR results according to RECIST criteria. Average duration of treatment was up to 40 months in the first group of patients Average duration of treatment was up to 28 months in the second group of patients.
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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 tumours 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 tumours, and to investigate the relationship between ghrelin, IGF2 and the clinicopathological characteristics.

Materials and methods
The study group included 77 patients diagnosed with adrenal tumours, included for adrenalnectomy. 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 1×10⁻⁸ M and 1×10⁻⁶ M significantly stimulated proliferation and migration in the H295R cell line.

Conclusion
Ghrelin may be involved in adrenal tumors development.

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P130

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 53.3(15.2). Histological classification was: 16(72.7%) well-differentiated neuroendocrine tumors (NETs) (8 pancreatic, 4 midgut, 2 lung and 2 unknown primary), 5(22.7%) paragangliomas and 4(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 parangangliomas. 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 treatement, 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 progression after a 12 months of treatment. Two patients had disease control after 12 months of therapy.

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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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 at AFP testing and safety.

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P131
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 79% received somatostatin analog treatment. Hepatic tumor load was 0% in 91%. 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< 0.001). 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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P132
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-ethylguanine-DNA methyletransferase (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, MSH2, MSH3, 6, PMS2 was assessed by multiple 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 to their role in creating neo-antigens similar to other solid cancers.

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P133
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...
and/or therapeutic target in 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 human 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 division 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 antitumoral action of the KiSS1 system 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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P134 Mesenchymal tissue markers as potential drug targets in adrenocortical tumours
to
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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 hallmark 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 markersSlug and N-cadherine were analysed by IHC. Expression of FGFR1-4 mRNA was quantified in FFPE tumour tissue using RNAscope and qRT-PCR array was employed to quantify expression of HGF-FGFR pathway genes. Isoform switching between isoforms IIIb (epithelial) and IIIc (mesenchymal) characteristic for EMT was assessed for 92 FGF-FGFR pathway genes. Isoform switching between isoforms IIIb and mitogen associated protein kinases in tumors compared with NAG. Interestingly, 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 tumours 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 FGF4 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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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).

In addition, we sought to study the potential functional role of this regulatory system in panNETs using human 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 division 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 antitumoral action of the KiSS1 system 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.

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 duodenopancreatic 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/hyomic 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. Treated steroid precursors in the media, [3H-P4 for 24 and 48 h lead to the time-dependent synthesis of the corticosteroid metabolites 17-hydroxyprogesterone (17-OHP4), deoxycorticosterone (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, allostericosteroid, and dehydrocorticoster- one (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 (NEs) 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 NEs that have visited the specialized, multipotent medical center of a University Hospital in Athens, Greece.

Methods

311 patients with NEs 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 NEs were female and 44.1% were male. The mean age at the time of diagnosis was 52.7±16.7 years old. The majority of NEs 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 NEs were regional at the time of diagnosis, 18.6% of patients had locally extended disease, while 25.4% of NEs, involving mostly NEs 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 NEs. Laboratory data revealed that CgA displayed 8 times higher risk for being metastatic at the time of diagnosis (OR=8.643, 95% CI=2.576-9.0).

Conclusion

This is one of the first large, epidemiological studies in Greece, evaluating the natural course of NEs through the experience of a specialized medical center. NEs 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 NEs.

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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, cau-la-tai 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 phaeochromocytomas-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 somatostatinoma 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 proceeded to a pancreato-duodenectomy of a dudodenal somatostatinoma 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. Conclusion

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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Introduction

MEN2A syndrome is one of the inherited multiple endocrine neoplasia type 2 (MEN2) syndromes comprising Medullary Thyroid Carcinoma (MTC) and Phaeochromocytoma (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 6/8 (range 16.9–390 ng/l). 3 of these 8 patients (17%) also had PCC at diagnosis (with elevated catecholamines/melanocortines). 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 609Y and codon C609R in Exon 10 in 3 patients each, followed by C609R and C604R in 1 each. All 3 patients with synchronous PCC and MTC at presentation had ATA 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 = 47 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 centrally 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 = 0.0084). In the high dose protocol group, 21 patients (64%) 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.

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P141
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 ≥ 18) 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%); sia: 4(9.5), thymus: 2(2.7%); breast: 1(1.4%) and cacium: 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.

Methods
Thirty-four patients with NENs and mBD were identified and included in the study.

Results
mBD therapy resulted in 1(1.4%) parotid gland 1(1.4%), ovaries and uterus 1(1.4%), pancreas 1(1.4%). 24(32.4%), adrenal gland 4(5.4%), lymph nodes 11(14.9%), retroperitoneal and pelvic implantation 2(2.7%), mediastium 2(2.7%), orbit 2(2.7%), brain 1(1.4%), parotid gland 1(1.4%), ovaries and uterus 1(1.4%), pancreas 1(1.4%). Sixty (28.1%) patients had Ki-67 ≤ 5% (grade 1), 25(15.8%) > 20% (grade 3) for gastro-intestinal NENs and for lung and thymus all (9.18%) 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 19 (17.6%). The imaging studies dentified mBD as following: 45(54/133) bone scan, 21 (35/60) MRL, 36/67(53.3%) CT, 35/54(64.8%) octreoscan, 11/21(52.4%) PET-PDG and 28/30 (93.3%) gallium-68 positron emission tomography (Ga-PET). The mBD therapy resulted in improvement in 63.5%, 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 ± 7.6(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 aim of the study was to assess the clinical features of gastric neuroendocrine neoplasms type 1 (GNE1). Methods
Fourteen patients (eight males) with mean age (± s.d.): 54.8 ± 12.4 years were recruited from two centers. Patients with documented disease progression were included in this study. Dedifferentiation was defined as histologically proven higher Ki-67 (%) able to increase the grade of neoplasm. Immunohistochemical analysis 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:>50%); metastatic sites included, only liver;6, liver and bone;1, liver and lymph node;2, 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 chemo therapy 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 ± 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 40% (4/10) 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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Female Reproduction

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 women 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 micropolyovarian 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
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 – tubulovillous adenoma with low grade dysplasia, 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 orectoide whole body scan and Spect CT- no uptake Treatment-BD mixed insulin, transfused to Hb>8 g/dl whipple pancreato-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 thyrotrph tumours, 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 thyrotrphinomas (FTT) and nine silent thyrotrphinomas (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 ± 2.6, P = 0.797; 3.94 ± 1.89 vs 2.27 ± 0.48, P = 0.207). 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 thyrotrphinomas 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 diagnosed 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 pheochromocytoma. At diagnosis, in 83% disease was disseminated. Hypercortisolism was diagnosed before neoplastic process in five cases. All patients presented rapid clinical evolution except for patient with pheochromocytoma. Weakness, hyperpigmentation, edema, hypertension and diabetes mellitus were the most important signs and symptoms. Two patients presented severe psychiatric disorders. Hypokalemia was observed in five cases (mean potassium level 2.35 mEq/l) and metabolic alkalosis in 4. Biochemical parameters were: cortisol 73 μg/dl (29.2–136.6), ACTH 561.1 pg/ml (46–1884), urinary cortisol 6596.9 μg/24 h (226–3,247), norepinephrine 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 milneprostone. No bilateral adenectomy were performed, only one adrenal embolization. Surgical removal of primary tumor was performed in two pancreatic tumors and pheochromocytoma, and four were treated with chemotherapy. Five patients died few months after diagnosis, pheochromocytoma 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.
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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 alkylation 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 alkylation chemotherapy of 6-cycles. 68Ga-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 alkylation 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, secondary 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

We present the case of a 36-year-old patient with no significant pathological personal history, diagnosed 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 chromogranin; 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 reinvention 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 chromogranin; negative synaptophysin, chromogranin and CD99, with positive CD56, NSE in lymph nodes and Ki67 20% in both sites. SSTR2 and SSTR5 receptors were also positive. A Tektiyotyl (99mTc-HYNIC-Tyr3-Octreotide) scan confirmed the presence of the radio- pharmaceutical 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 x 15 mm “nodule” 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 psychiatric 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 x 25 mm). She had undergone right adrenalectomy (histopathologic exam and immunohistochemistry confirmed the diagnosis) and received one year of treatment. However, cortisol levels increased after one year and she was previously diagnosed (in 2008) with ACTH-independent Cushing’s syndrome due to a cortisol secreting adenoma of the right adrenal gland. She had undergone right adrenalectomy (histopathologic exam and immunohistochemistry confirmed the diagnosis) and received one year of treatment.

Conclusion
The association between ACTH-independent Cushing’s, schwannoma finding in the same adrenal gland 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 paranganglionic 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 SDHBI, 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 SDHBI 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 SDHBI 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 malignancy rate: 15% of the cases.

Conclusions
In the HNPG in our series, the most frequently found mutation was SDHBI, 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 paranganglionic 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 asthma 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 (HD, SDH and VHL) create a similar effect to the stimulation of paragangliotic 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.

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 anthropometric parameters and their 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 adenosas producing 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, WHR). The data were statistically analyzed by STATISTICA 12. a = 0.05. The average BMI was 29.5±5.3 kg/m², WHR (women) 0.9±0.2, WHR (men) 1.0±0.1, WHR 0.6±0.1, BAI (women) 35.1±6.2, BAI (men) 21.6±3.0%, VAI 2.1±0.3. The average systolic pressure was 142±18 mmHg, diastolic pressure 83.2±19.5 mmHg. The mean concentration of 25(OH)D3 was 18.6±7.7 ng/ml, 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<0.05) 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), WHR and TG (r=0.04). Systolic pressure was statistically higher (p<0.05) in patients with higher BMI (r=0.11), BAI (r=0.06), WHR (r=0.09), WHR (r=0.14). Fasting glucose correlated posittively (p<0.05) with BAI (r=0.05), BMI (r=0.11), VAI (r=0.03), WHR (r=0.13). WHR (r=0.16), HBA1C% (p<0.05). Patients with higher 25(OH)D3 concentration had statistically lower HBA1C%, TC and LDL cholesterol (p<0.05). There were negative correlations (p<0.05) between HDL cholesterol and VAI, WHR, WHR. Low 25(OH)D3 concentration may indicate lipid disorders in patients with non-functioning adrenal incidentalomas. BMI, BAI, VAI, WHR and WHR are good indicators of metabolic syndrome in studied group of patients with non-functioning adrenal adenomas.

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Paediatric endocrinology

P156

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 androgeners 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 hyperplasia, mainly due to 21-hydroxylase 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 hypotension and more than half had mucocutaneous hyperpigmentation, asthma, anorexia, weight loss, nausea 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 50% were also on fludrocortisone (mean dose 0.5 ± 0.2 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 ± 6 years. Cranopharyngioma 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 ± 2.8 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.

P157

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-9a-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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P158

Gender differences in delays to diagnosis of acromegaly: data from the Swedish National Patient Register

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Acrromegaly 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 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 underlies 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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P159
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 £6 086 (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. SSA (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% in 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 155% 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

P160
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. Irreversibly, 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 analyse 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 (20-40mg/daily) 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 (11β, 18α-dihydrocortisol and 11β-OH-etiocholanolone) were similar in patients and controls. The urinary THF+5xTHF/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), THF/2xTHF (P<0.001) and androstenedione/etiocholanolone (P=0.023) ratios were higher in patients suggesting a lower 5α-reductase activity. Similarly, ratios evaluating 5α-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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P161
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/l24 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 unilater., 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/ml 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 cancer
P163

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 (≤10 mm), with serum calcitonin < 1000 pg/ml. In all patients, sentinel-LN mapping was performed by injecting 1% MBD subcapsulary 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 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 prophylactic lateral neck dissections. This screening could avoid the triggering of an adrenal insufficiency in thyroid hormonal substitution.

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Poster Presentations: Calcium and Bone
Bone & Osteoporosis

P164

Influence of the levels of vitamin D on T-score in HIP measured by DXA of colombian postmenopausal women

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Results

124 Postmenopausal women were included at mean age of 66.07 ± 11.26 years; with average levels of serum calcium:9.53 ± 0.60 mg/dl; mean of parathormone:57.06 ± 27.14 pg/ml; mean vitamin 25(OH)D:25.69 ± 9.22 ng/ml; mean serum phosphorus: 3.62 ± 0.61 mg/dl; mean hip T-score: -1.92 ± 1.18; mean hip Z-score:0.958 ± 0.80; hip bone mineral density:0.833 ± 0.095 g/cm²; 22.08% of patients had a deficiency of 25(OH) vitamin D and 53.25% had insufficiency of 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 overweight 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 tissue on bone mineral density.

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P165

Potential extension of frax algorithm 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 major cause of disability and mortality, for millions of people worldwide. Frax is an algorithm that relies on a questionnaire for the prediction of bonefracture. This algorithm 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 fractures 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 the last year we have enrolled 1132 patients at the Unit of Endocrinology, Diabetes and Metabolic Diseases at the University Hospital of Tor Vergata, Rome, Italy. All subjects underwent to evaluation of anthropometric data (weight, BMI, height), bone densitometry with DXA A 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. ± 0.630±0.818 g/cm² ±0.07), 712 with osteopenia (−1.74 ±0.42±0.649 g/cm² ±0.05) and 210 with osteoporosis (−2.86 ±0.38±0.315 g/cm² ±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 overweight 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 tissue on bone mineral density.

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P166

A case report: FGFR3-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)2D3. 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 trauma department. Analysed 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 osteostabilization by adipocytes of bone marrow and stimulation of proinflammatory cytokines synthesis leads to increased bone fragility without decreasing BMD.

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P169

Effect of surgery vs observation: 6-Year skeletal outcomes in primary hyperparathyroidism
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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.

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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 osteostabilization by adipocytes of bone marrow and stimulation of proinflammatory cytokines synthesis leads to increased bone fragility without decreasing BMD.

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P170

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 healthy 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/m². 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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P171

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 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 BMI was 30.3 ± 6.3 kg/m$^2$. In age and BMI adjusted models, there was an inverse correlation between trabecular area at 4% site [$r = -0.58; P = 0.003$]; 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 [$r = -0.49; P = 0.018$] 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 ([$b = -0.567; 95\%$ 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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P173

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.

Materials 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.

Different values were considered significant for $P < 0.05$.

Results

FGF23 was within the reference ranges (120 ± 30 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 regulates its role may be largely replaced by PTH in primary hyperparathyroidism.

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P174

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/cm². T-score was –1.2 SD. BMD and lumbar vertebrae T-scores for a single lumbar vertebra were: L1 1.384 g/cm², –4.2 SD; L2 0.667 g/cm², –3.3 s.d.; L3 0.654 g/cm², –3.9 s.d.; L4 0.785 g/cm², –3.0 s.d. The BMD and T-score of the neck were 0.463 g/cm², –3.5 s.d. and of the total hip 0.590 g/cm², –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/cm², T-score was –3.4 s.d. BMD and T-scores were: L2 0.614 g/cm², –3.8 s.d.; L3 0.642 g/cm², –4.0 s.d.; L4 0.785 g/cm², –3.0 s.d. In 2018, BMD of analyzed lumbar spine (L3-L4) was 0.911 g/cm², T-score was –1.7 s.d. BMD and T-scores were: L3 0.976 g/cm², –1.0 s.d.; L4 0.845 g/cm², –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 fractures, osteophytic 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. DOI: 10.1530/endoabs.56.P175

P175

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, PINP,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/m²) and 104 control subjects (mean age 54.06 years, mean 28.4 BMI kg/m²) 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-I (244.5 ± 148.2 vs 115.2 ± 37.7 ng/ml; P < 0.0001) and PINP (55.69 ± 34.3 vs 45.47 ± 18.6 ng/ml; 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 PINP (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-I was observed.

Conclusions

In this study, acromegaly patients had lower TBS and LS BMD than healthy controls. Additionally, those with VFs had lower TBS, and PINP, 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. DOI: 10.1530/endoabs.56.P175

P176

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 the occurrence of AFF. 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 continuously treated with various type of bisphosphonates without any therapeutic pause or medical control. At that moment an association between bisphosphonates long term use and the occurrence 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 full recovery of the mobility and an increase in the quality of life. While concrete evidence based recommendations cannot be provided, strict surveillance, overall awareness of prodomal thigh pain, radiological findings and bisphosphonates usage records are recommended 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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P177

Malignant hypercalcaemia 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 hypercalcaemia have also been
described, one of moderate hypercalcemia following denosumab discontinuation 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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P179
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 sagittal 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). Hypoechoic regions on ultrasound(US) were matched with chief cells in 21 (55.3%), oncocytic cells in 21 (55.3%), cystic 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 isoechogenic areas (P<0.05). Lipoic tissue ratio was significantly less in hypoechoic areas than hyperechogenic areas (P<0.05). There was no significant difference between echogenity, 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 cystic area ratio and chief cell amount in atypical and other cases(P>0.05). A moderate positive linear relationship was found between serum calcium levels and cystic 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, hyperechogenic areas of US images were matched with chief cells, hyperechogenic areas were compatible with connective and adipose tissues in histopathology. The positive linear relationship between serum calcium levels and cystic 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 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 recipients.

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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 I n-terminal propeptide (PINP) and beta-crosslaps in 64 (32 men) consecutive patients, median (25, 75 percentile) age 61 (49.5, 65.5) years, on permanent hemodialysis.

Results
Median (25, 75 percentile) PTH, osteocalcin, PINP 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, PINP and beta-crosslaps results respectively were higher 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 PINP (r=0.6898, P<0.001). There was no correlation between PTH and bone resorption marker beta-crosslaps (r=-0.1520, P=0.23).

Conclusion
Bone turnover is increased in end stage renal disease. Beside PTH, osteocalcin and PINP 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 99mTc-sestamibi for localization of parathyroid adenomas
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99mTc-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 123I/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 subsequent parathyroid surgery was performed. Pre-, post- surgical and biochemical workup of HPTH, surgical pathology reports were analyzed. Correlative imaging with 123I/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 parathyroideectomy 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). PTH levels were in deficient range. Vertebral fractures mostly observed in 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 normal 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 recipients.

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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 microarchitecture 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).

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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, Mergimac, 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/m2 in patients with acromegaly vs 26.7 (95% CI 25.3–28.1) kg/m2 
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/sm2 (95% CI 1.100–1.225) vs 1.221 g/sm2 (95% CI 1.149–1.293); BMD T-score L1-L4 measurements compared to the control group: BMD L1-L4 1.162 g/sm2 (95% CI 1.100–1.225) vs 1.221 g/sm2 (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. BMD 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 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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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), adipokines (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.

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 thyroid disease or hematologic malignancy. Herein, this case highlights HOA as a rare presentation of celiac disease.

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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/cm² (T-score = −1.2), femoral total: 0.79 g/cm² (T Score = −1.6), and lumbar total: 0.70 g/cm² (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/cm²).

Conclusion

Bisphosphonates are one of the most widely prescribed drugs for the treatment of 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 bisphosphonate 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 antiresorptive 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 18F-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 3.9×3.3×3.5 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 disease 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/m² 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 naive. 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 previous BP use. The 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 hydrenephrosis. Chest radiographs showed severe sclerosis with marked dysmorphism of the scapulae, the humerus and the clavicles. Laboratory evaluation revealed low serum ALP levels (11 U/I; n.v. 40–150) and high values of Vitamin B6 (33.5 μg/dl; n.v. 7.8–27.2), consistently with a diagnosis of HPP. Serum PTH was high (94.20 pg/ml; n.v. 8–76) and 25OH-vitamin D low (1.48 mmol/l) were within normal range, but parathyroid hormone investigated. Patients plasma calcium (2.24 mmol/l) and phosphorus (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 sensorineural 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 zoleodronate 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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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 spondilolisthesis as well as progressive hearing impairment and dizziness was referred 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 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 hydrenephrosis. Chest radiographs showed severe sclerosis with marked dysmorphism of the scapulae, the humerus and the clavicles. Laboratory evaluation revealed low serum ALP levels (11 U/I; n.v. 40–150) and high values of Vitamin B6 (33.5 μg/dl; n.v. 7.8–27.2), consistently with a diagnosis of HPP. Serum PTH was high (94.20 pg/ml; n.v. 8–76) and 25OH-vitamin D low (1.48 mmol/l) were within normal range, but parathyroid hormone investigated. Patients plasma calcium (2.24 mmol/l) and phosphorus (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 sensorineural 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 zoleodronate 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.

Conclusion

We report a novel missense mutation of TNSALP gene, causing late-onset HPP. 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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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 (OHIO) 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 vertebralae, 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/cm² (T-score —4.8), hip neck 0.507 g/cm² (Z-score —2.9) and hip total 0.496 g/cm² (Z-score —3.6). Other causes of secondary osteoporosis were excluded and the antosteoporotic 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 (Z-score 3.6). Other causes of secondary osteoporosis were excluded and the antosteoporotic treatment with denosumab was started. The patient was first seen by an endocrinologist in October 2016 because of progressing symptoms.

Discussion

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 2.0 cm size tumor between rectus femoris and tensor fasciae latae. In December 2017 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, crosses, 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/m² (U = 190.5, P = 0.61), duration of menopause, years (U = 146.5, P = 0.008). 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 = 4.2, P < 0.0001; phosphorus 0.9 (0.80-1.06) mmol/l vs 1.36 (1.32-1.40) mmol/l in the control group, U = 0.01, 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 (85.5-144.3) pg/ml vs 11.12 (35.4-53.3) 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 = 2, P = 0.07; crosses 0.60 (0.37-0.79) mmol/l 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, crosses. We detected negative correlation between OPG level and calcium total r = -0.6, P < 0.05, r = -0.7, P < 0.05, PTG r = -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) from 2011 to 2017. Each patient had a phosphocalcic balance, a vitamin D test and OPG, vitamin D, BMD measurements in the lumbar spine, femoral neck, total hip, and distal 1/3 radius by DXA (T-score33%, BMD33% g/cm²).

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/m² (U = 196.5, P = 0.61), duration of menopause, years (U = 146.5, P = 0.008). Osteoporosis of distal 1/3 radius was founded in 33% (10 cases), osteopenia in 43% (13 cases) in postmenopausal women with PHPT(T-score33%, BMD33% g/cm²). Significant differences was detected in the distal radius BMD in 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, alkaline phosphatase, PTG, OPG, crosses, osteocalcin.

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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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, alkaline phosphatase, PTG, OPG, crosses, 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/m² (U = 196.5, P = 0.61), duration of menopause, years (U = 146.5, P = 0.008). Osteoporosis of distal 1/3 radius was founded in 33% (10 cases), osteopenia in 43% (13 cases) in postmenopausal women with PHPT(T-score33%, BMD33% g/cm²), and low distal radius BMD was no founded in the control group (T-score33% = -0.3 (-0.7 –0), BMD33% = 0.87 (0.82-0.9) g/cm²). Significant differences was detected in the distal radius BMD in postmenopausal women with PHPT compared postmenopausal women without PHPT (U=22.0, P < 0.0001, U=BMD33%= 20.5, P < 0.0001). We detected correlation between OPG level and distal radius BMD: r=0.05, r=0.05, U=BMD33%= 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.
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 10th 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/cm² (T-score: –2.5) for lumbar spine, 0.783 mg/cm² (T-score: –1.4) for neck and 0.783 mg/cm² (T-score: –1.3) 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 spine BMD increased to 0.882 mg/cm² (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 (79.5 ± 8.5 vs 75.1 ± 7.9, P < 0.273. 1 vs 3+ 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. Microangiopathy and MetS seems to affect negatively to BMS.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>T1D</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>38.4 ± 9.9</td>
<td>39.3 ± 10.3</td>
<td>0.729</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>24.7 ± 4.5</td>
<td>25.3 ± 4.9</td>
<td>0.617</td>
</tr>
<tr>
<td>T-score, lumbar</td>
<td>–0.10 ± 1.2</td>
<td>0.05 ± 1.1</td>
<td>0.296</td>
</tr>
<tr>
<td>T-score femoral neck</td>
<td>–0.5 ± 0.9</td>
<td>0.67 ± 1.0</td>
<td>0.624</td>
</tr>
<tr>
<td>CMS</td>
<td>80.5 ± 7.1</td>
<td>79.9 ± 8.5</td>
<td>0.825</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.54 ± 0.3</td>
<td>9.61 ± 0.4</td>
<td>0.653</td>
</tr>
<tr>
<td>iPTH (pg/mL)</td>
<td>36.2 ± 14.6</td>
<td>44.3 ± 28.1</td>
<td>0.542</td>
</tr>
<tr>
<td>Calcidiol (ng/mL)</td>
<td>26.0 ± 11.4</td>
<td>25.2 ± 11.9</td>
<td>0.818</td>
</tr>
</tbody>
</table>

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P198

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 = 0.399, respectively) and free androgen index values (R = 0.150 and R = 0.270), 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 in women with menstrual disorders seems to be blurred. As a result, determination of body fat distribution in patients with ovarian insufficiency may be of lesser clinical importance.

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P199

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 genu varus, 10 (45%) patients with genu 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 884 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 g/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 immediately after the race were determined the following parameters: insulin, glucose, uric acid and creatinine by standard methods; IL-6-plasma and cytokine-plasma.

Results
The genotype’s frequencies of polymorphisms analyzed were: LEP (homozygous G 0.29, heterozygous 0.51, homozygous A 0.20), ADRB2 (homozygous G 0.51, heterozygous 0.25, homozygous Arg 0.07) and BGLAP (homozygous T 0.60, heterozygous 0.31, homozygote C 0.09). The alleles 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 and waist circumference 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 % Gla-OC (β = 0.041) and Δ% Gla-OC (β = 0.037). In 9-courses completers, LEP-A carriers presented a gain increase in % Gla-OC (β = 0.012). For the ADRB2 polymorphism, alleles with AG + GG genotypes
Conclusion
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 = 25.61 ± 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%: [1.09-4.342]) 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 and AP_BF and total cholesterol for DHFR_ins/ms 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_ins/- 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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Calculus & 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) Bangladeshi 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 slighty 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-D9k expression in rat cerebellum
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Introduction
Calbindin-D9k is a 9 kDa polypeptide expressed in the mammalian intestine, uterus, and pituitary gland. Calbindin-D9k increase Ca\(^{2+}\) absorption by buffering intracellular Ca\(^{2+}\). The intracellular concentration of calcium is regulated by calcium related proteins such as calbindin-D9k, TRPV1 and PMCA1. The regulatory effect of steroid hormones and glucocorticoids on calbindin-D9k, TRPV1 and PMCA1 expressions in the cerebellum are currently unknown. In this study, we investigate the expressions of calbindin-D9k, 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-D9k, TRPV1 and PMCA1 expressions, 14 days old rat were administered 40 µg/kg of E2, 20 mg/kg of P4, 10 mg/kg of ICT 18:2-780 and 13 weeks old rat were administered 10 mg/kg of Dexamethase (Dex), 50 mg/kg of RU486.

Results
Transcriptional level and localization of Calbindin-D9k, TRPV1, PMCA1 were examined in the cerebellum. mRNA and protein level of Calbindin-D9k was increased by Dex, but not by E2 nor P4. Immunofluorescence shows that calbindin-D9k were mainly localized in the purkinje cell. Like the expression of increased by Dex, but not by E2 nor P4. Immunofluorescence shows that calbindin-D9k, TRPV1 and PMCA1 expressions are 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.

Conclusion
These results are correlated with calbindin-D9k, 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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**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 shown 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 EDCs 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 E 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 receptive and implantation adhesion and invasion.

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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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**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 ≥ 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 ≤ 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 = 5.39, 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%, 35%, 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.
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 = 0.0003 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 = 0.009 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 radiiodine therapy induced hypercalcemia in Graves’ disease: Case series
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Introduction
Graves’ disease (GD) is often treated with radiiodine therapy for cure. While, post external irradiation and post-radiiodine therapy (RAI) induced hyperparathyroidism after many years of latency is a well known phenomenon, there are only anecdotal reports of post-radiiodine hypercalcemia. 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 normocallmic 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
66/5 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, Thyroid-ectomy, Radiodine, 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 PHPT, 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 mmol/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 nephro lithiasis, 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 = 0.005) and PTH (1.7 ± 2.1 X UNL, P = 0.05) at last follow-up. The younger patients had more nephro lithiasis (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 ± 0.4, 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.

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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 GI symptoms. Dental manifestations as primary or presenting findings 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 normocalcemic.

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 (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-presence 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-hydroxvitamin 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; 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) ($P<0.05$). The 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 0.1 to 0.2 per 1000 population in the period from 1980 to 1984 to 0.38 to 0.88 per 1000 population in the period from 2010 to 2014.

**Conclusions**

The incidence of PHPT in Santander continues its remarkable rise. The incidence in the period from 1995 to 1999 was 2.75/100,000 person-years. The prevalence of diagnosed PHPT in Santander increased from 0.1 to 0.2 per 1000 population in the period from 1980 to 1984 to 0.38 to 0.88 per 1000 population in the period from 2010 to 2014.

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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-subunit 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 sensitivity 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 (SHPT) due to chronic renal failure were used as controls. hCG β-subunit kit on Cobas (Roche Diagnostics) uses 2 monoclonal antibodies that recognize hCG β-core, linked to enzyme and free β-subunit. Limits of hCG detection and quantification are <0.1 and <0.6 mIU/mL. In non pregnant and postmenopausal women and in men, hCG (g95%) is <1 (5.3), <7 mIU/mL (8.3) and <2 (2.6) mIU/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 PHPT (1.25 UI/L) and SHPT (0.97 UI/L). hCG test sensitivity was 75% and specificity was 94% to detect parathyroid cancer, with a cut-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 sensitivity of 75% and a specificity of 94%. The only patient still alive who underwent a PTH immunotherapy, presented the lowest hCG values. 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**

**Reliability of serum Calcium to Phosphorus (Ca/P) ratio as an accurate and inexpensive tool to 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 hypophosphatemia (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.
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%, 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 10 with elevated serum creatinine. We defined SHPT as PTH >7.0 pmol/l and 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.

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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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 6–12 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, heterogeneous recipient population and variations 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; 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 1st, 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.

Reference

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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 nmol/l and <20 nmol/l, 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 (± s.e.m) 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) 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
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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 normophosphatic 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 25OHID < 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, calcitriol: 180.3 ± 123 mg/dL/24 h, PTH: 117 ± 42 and 25(OH) vitamin D: 14.86 ± 3.3 ng/mL. After treatment with vitamin D there was a significant increase of 25(OH) vitamin D levels (0.36 ± 19, P < 0.0001) and a significant decrease of PTH levels (0.24 ± 70, P < 0.0001), serum calcium (9.8 ± 0.25 mg/dl, P < 0.037), and calcitriol (199 ± 123 mg/dL/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 hyperparathyroidism diagnosis in vitamin D deficiency must be calculated.

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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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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 microthiasis and prostate neoplasia, 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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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 need 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, tetyan, 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.

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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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, nephrocalkinosasis, kidney stone, kidney failure, depression and anxiety. Objectives

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 hypocalcaemia 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 mg2/dl2, and 98.4% had a calcium-phosphate product under 55 mg2/dl2. Hypercalcuria 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 hypocalcaemia 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). Nephro lithiasis was detected in 14.6% and nephrocalkinosasis in 2.3% of the cohort. Soft tissue calcifications were observed in 14.6% of the cohort. Bone fractures occurred 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

Hypoparathyroidism and its treatment are associated with a high rate of complications, particularly kidney disease.

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Clinical manifestations of Hypomagnesaemia and Hypocalcaemia: an unmonocentric cohort

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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. Vitamin D deficiency may also be correlated with secondary hyperparathyroidism. A hip fracture and vitamin D deficiency can be correlated with secondary hyperparathyroidism. A hip fracture and vitamin D deficiency can be correlated with secondary hyperparathyroidism. 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. Vitamin D deficiency may also be correlated with secondary hyperparathyroidism.
Primary hyperparathyroidism (PHPT) is rare when associated with 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) type 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, hepatoplenomegaly, moderate anemia and acute renal failure. His history included 3 AP attacks managed conservatively throughout the last 2 years, left renal micro lithiasis, 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) level (320 pg/ml), high serum amylase (167 U/l), lipase (318, 8 U/l), C-reactive protein (9.94 mg/dl), azotemia (creatinine = 1.75 mg/dl, serum urea = 47 mg/dl), hyperglycemia (130 mg/dl) and moderate anemia (haemogoblin = 9.3 g/dl). Ultrasound showed a 5.8/4.0/3.7 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, hydration, 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 hypocalcemia 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 recurrence.

P225
Primary hyperparathyroidism due to a parathyroid adenoma with cystic degeneration presenting as recurrent acute pancreatitis

P226
Glucose metabolism in primary hyperparathyroidism: The role of cystic parathyroidectomy

P227
Acquired Fanconi syndrome and hypophosphatemic osteomalacia in two patients treated with adefovir and tenofovir

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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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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-operative 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 (≥ 11 mg/dl or ≥ 2.75 mmol/l, amounting to 10-30 mg/day; or ≤ 11 mg/dl ≤ 2.75 mmol/l = mg/day). 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 66.1±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. 118.3±33.5 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 tendedly decreased in both groups. Conclusion
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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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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Methods
Initially, 17 patients with documented pHPT were recruited and treated with calcimimetic cinacalcet at a dose calculated according to s-Ca levels (≥ 11 mg/dl or ≥ 2.75 mmol/l, amounting to 10-30 mg/day; or ≤ 11 mg/dl ≤ 2.75 mmol/l = mg/day). 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 66.1±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. 118.3±33.5 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 tendedly decreased in both groups. Conclusion
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 (PHT). PHT 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 m2), as were the 24-h urinary calcium concentrations 189 mg/24-h (normal range: 50–300). Dual-energy X-ray absorptionmetry (DXA) in lumbar spine was indicative of osteopenia (T-score: –2.3). Renal ultrasound was negative for the presence of kidney stones. Primary (PHT) 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.
P231
Assessment of calcium and vitamin D medications adherence in patients with hypoparathyroidism after thyroidecmy
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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 your 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 polyuria. Of these, 10 (15.6%) patients left medication due to these side effects.

Conclusion
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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P232
Preoperative serum vitamin 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-D3, 25OH-D2) 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 characteristics 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 (P = 0.26, P = 0.03) and Ki67 levels (P = 0.27, P = 0.02) but did not correlate with tumor size (P = 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Benign Group</th>
<th>Cancer Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>64</td>
<td>96</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.80 ± 12.21</td>
<td>58.51 ± 11.95</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>27.78 ± 5.86</td>
<td>28.98 ± 5.17</td>
<td>0.18</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>89.62 ± 14.63</td>
<td>93.80 ± 13.10</td>
<td>0.03</td>
</tr>
<tr>
<td>Hip Circumference (cm)</td>
<td>104.45 ± 12.46</td>
<td>107.00 ± 11.13</td>
<td>0.10</td>
</tr>
<tr>
<td>Waist-to-Hip ratio</td>
<td>0.86 ± 0.08</td>
<td>0.88 ± 0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>36.93 ± 8.34</td>
<td>39.22 ± 9.57</td>
<td>0.07</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>100.11 ± 16.99</td>
<td>108.03 ± 26.47</td>
<td>0.09</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>255.19 ± 259.71</td>
<td>214.98 ± 41.61</td>
<td>0.14</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>99.61 ± 47.75</td>
<td>109.38 ± 52.24</td>
<td>0.22</td>
</tr>
<tr>
<td>Vitamin D3 (ng/ml)</td>
<td>19.52 ± 9.67</td>
<td>18.94 ± 11.17</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Reference

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P233
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 (FEV₁) 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 FEV₁ (95% CI: 0.03 to 1.98) and 1.02% predicted higher FVC (95% CI: 0.26 to 1.77). In women no association between serum 25(OH)D and FEV₁ (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 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 FEV₁, FVC, and IL-6.

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 (25(OH)D) is considered the most reliable marker of vitamin D status. Adequate levels 25(OH)D 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 bihemoral characterization. The analyses of 25(OH)D by chemiluminescence immunoassay (DiaSorin LIASON) and HPLC-MS-MS were performed at the same moment from two aliquots of the same stored sample. 25(OH)D levels with LIASON were statistically lower than with HPLC-MS-MS (17.6 ± 8.9 nmol/L 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 LIASON (5% vs 63%, P < 0.0001). The same result was found for severe Vitamin D deficiency (< 25 nmol/L or 10 ng/ml) vs 25.4% vs < 0.0001). A good correlation (R = 0.909, R² = 0.824, P < 0.0001) between 25OH2D values measured with LIASON and with HPLC-MS-MS was found. The inter-assay bias was evaluated by Bland-Altman plots: compared to the HPLC-MS-MS method, LIASON 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 25OH2D measurement.

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P235

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 measurement 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 (20.83 ± 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, MaFright: 912.00 ±226.6 N vs 870.14 ±127.9 N, P = ns). Conussion
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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P236

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 connected at the moment. The clinical, biochemical, radiological and hemopathological factors of PHPT patients were analyzed for similarity connected at the moment.

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) nephro lithiasis and/or decrease in glomerular filtration rate (25%), cardiovascular complications (59%), upper gastrointestinal lesions (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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Endocrinology Research Centre, Moscow, Russian Federation.

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 parathyroid 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 hyperphosphatemia. He had been treated with cinacalcet 120 mg and sevelamer 4800 mg per day and his laboratory findings were as follow: calcium (Ca) – 2.92 mmol/l (range 2.1–2.55 mmol/l), PTH – 117 pg/ml, P – 0.53 mmol/l. Five months after start of treatment, the patient had a progressive increase of bone density on densitometric examination. No other PG were identified. During a surgery, an 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 intrathyroidal parathyroid tumor was detected that had no clear boundary with the right upper PG and intrathyroidal parathyroid tumor. During a surgery, an 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 intrathyroidal parathyroid tumor was detected that had no clear boundary with the right lobe of the thyroid gland.

Discussion

Ralofoxine 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 pseudohyoparathyroidism

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Pseudohyoparathyroidism (PHP) is group of heterogeneous disorders characterized by hypocalcaemia, hyperphosphatemia and elevated parathormone (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 1 (A, 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 falk (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%) neuropsychiatric 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 or MRI during follow-up.

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P240

Thyroid oncocytes may complicate 18F-fluorocholine PET-CT localization of parathyroid adenomas in primary hyperparathyroidism

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18F-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 99mTc-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. 18F-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 18F-fluorocholine imaging (false negative). In 2 patients, 18F-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 18F-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 18F-fluorocholine has been documented in oncocytic thyroid adenoma. In all patients (3 of 9) with inconclusive 18F-fluorocholine PET-CT imaging either oncocytic thyroid cells or oncocyctic metaplasia were found by aspiration cytology or postoperative histopathology. In our study sample, 18F-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 18F-fluorocholine PET-CT parathyroid imaging. Further studies are needed to evaluate 18F-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 = 152]. 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 59.5 ± 14.3 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 ± 6.6 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 ng/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 ± 152.1 initially and 164.7 ± 16.6 pmol/l at the end of observation, P = 0.573. 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 nmol/l, 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 (2.8%) and in North Africa it requires repeated transfusions. Life expectancy has been dramatically improved and patients are living 20 to 40 years which are the modality of life for the major thalassemia patients. Major Beta Thalassemia (MBT) patients are at high risk for developing iron overload, osteitis fibrosa cystica, and parathyroid adenomas which can lead to more severe bone disease. 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.

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 and group B patients with 25-OHD concentrations < 20 ng/ml. 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). The prevalence of asymptomatic HPT was 25%, normo-calciemic 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 the most and the others have a good control of the disease.

Conclusion
Vitamin D deficiency is a common disorder in patients with HPTP. It seems to be more severe bone disease. Our results suggest that there is not an effect of vitamin D deficiency on parathyroid tumour 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 iso- tope 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 suggesting 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 and 97% had symptomatic hyperparathyroidism. 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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Recent hyperparathyroidism (HPT) refers to reappearance of hypercalcaemia 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 hypercalcaemia after surgical interventions for pHPT.

Case 1: A male patient, MI, 47 yo, had recurrent hypercalcaemia 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 hypercalcaemia 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, his calcium remained stable in the high normal range and his calcium was 340 pg/ml. Sestamibi parathyroid scintigraphy and ultrasound scan 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 rests. In conclusion, in some cases, it should make a distinction between a locoregional metastatic parathyroid carcinoma with multiple implants and parathyromatosis.

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P249

Prenatal hypophosphatasia with severe skull bone deficits

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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, 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 (45.6%) 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. Aledronate was the most commonly adopted medical treatment.

Conclusion
To the best of our knowledge, this important endocrinial 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-medistinal 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 and 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 expertise 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). PHT 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 hypercalcaemia.

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±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 hypocalcemic hyperparathyreosis (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 second 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 hypertension – galactorrhea syndrome (last menstrual cycle 10 years ago). The serum levels of TSH was slightly elevated (8.8 mU/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 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 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/m²) treated with sleeve gastrectomy. All patients received standard supplementation of vitamin D before and 1 year after surgery. Blood 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 = 0.7, P < 0.0001). 25-OH-vitaminD showed an inverse correlation with PTH levels (r = -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/m²), 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 = -0.60, P = 0.002 and r = -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 sensitivity of contrast-enhanced ultrasound (CEUS) in the detection of pathological parathyroid glands in patients with primary hyperparathyroidism in comparison to the 99mTc-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 99mTc-MIBI-SPECT scintigraphy. Moreover using CEUS, double adenomas could be detect in 1 of 2 cases. All 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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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 proportionally 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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**P257**

**Primary hyperparathyroidism after thyroid surgery and autotransplantation 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 brachialradial muscle can be performed in case of intratumoral passage 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 calcitomin, 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 urinary calcium of 830 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 thyroidecmy, 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 surveillance of serum calcium and PTH levels.

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**P258**

**Metabolic encephalopathy following intravenous zolendronate for hypercalcemia 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 underwent surgical intervention with left hemithyroidectomy and left lower part of left thyroid lobe. Parathyroid scintigraphy resulted with parathyroid adenoma. A CT scan of the neck confirmed a supraclavicular 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 hypercalcemia. Hypertension may or may not remit after successful parathyroidectomy. We will follow this patient to evaluate hypertension remission.

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**P259**

**Primary hyperparathyroidism: a rare cause of hypertension?**

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**Background**

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), parathyromone (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 supraclavicular 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 hypercalcemia. 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 nephrolithiasis**

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**Introduction**

Primary hyperparathyroidism (PHPT) is a rare disorder among young adults. Classic manifestations of PHPT, such as nephrolithiasis, are rare seen today.

**Case report**

We refer the case of a male young, 25 years old, presented in emergency unit with: headaches, lumbago, epigastric pain, weight loss (5 kg during six last months), polyuria-polydipsia. Medical history: He has been diagnosed with nephrolithiasis and gastritis a year ago. Negative family history. Blood biochemistry: Ca²⁺ = 2.3 mmol/l (N1.3–1.7 mmol/l), total calcium 17.6 mg/dl (N8.5–10.5 mg/dl), Phosphorus 2 mg/dl, Mg²⁺ = 1.5 mg/dl, Hct 35.3%, Hgb11.3 g/dl, WBC: 5900/mm³, urea: 69 mg/dl, creatinine 1.6 mg/dl, sodium 144 mmol/l, potassium 3.7 mmol/l, glucose 83 mg/dl, ALT 11 U/l, AST 14 U/l, GGT15 U/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 nephrolithiasis. 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 ultrasonography: Right thyroid lobe normal, Left thyroid lobe with a well-restricted (16.3 ng/dl). We suspected a parathyroid gland disease, so we performed, Thyroid ultrasonography: Right thyroid lobe normal, Left thyroid lobe with a well-restricted expansione, reduced echogenicity, sized 16×6 mm, with posterior acoustic shadow. We refer that a parathyroid adenoma, which is situated in the left lower lobe. We performed parathyroid scintigraphy revealing a lesion in the left lower thyroid lobe.

**Discussion**

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.

**Conclusion**

Most patients with primary hyperparathyroidism are asymptomatic, but others may present with symptoms related to chronic hypercalcemia, such as hypercalcemia. Hypertension may or may not remit after successful parathyroidectomy. We will follow this patient to evaluate hypertension remission.

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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 confirms 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 hyperparathyroidism 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

Forty-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 with calcium metabolism. Preliminary results were 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 were presented in this article, we continue to the study.

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Clinical Case Reports - Thyroid/Others

P263

Severe hypercalcemia due to atypical parathyroid adenoma

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Introduction

Primary hyperparathyroidism 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 weaknesses for 1 month. Her past medical history was nonsignificant. She denied urinary tract infection and no history of gout. Her last menstrual period was 3 months ago. She never used hormonal contraceptives. On examination: BMI 29.07 kg/m2, BP 173/99 mmHg, heart rate: 89, mild 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 mIU/ml, LH 0.85 mIU/ml, free testosterone 0.76 mg/dl, FT4 0.62 ng/ml, TSH 0.58 mg/ml prolactine 12.1 ng/ml. 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 haemangiomata 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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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 µg/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 upright 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/m², 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 Cushings’ syndrome workup. The lab tests: ACTH 98.30 pg/ml, FSH 1.28 mIU/ml, LH 0.85 mIU/ml, free testosterone 0.76 mg/dl, FT4 0.62 ng/ml, TSH 0.58 mg/ml prolactine 12.1 ng/ml. 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 haemangiomata 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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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, hypokalaemia, 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), hypokalaemia (potassium, 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), hypokalaemia. He had electrocardiogram abnormalities (prolonged QT interval, preexcitation supraventricular tachycardia). After exclusion of possible causes, hypomagnesaemia secondary to PPI was diagnosed and omeprazole was stopping. Hypomagnesaemia is often associated with hypokalaemia (due to urinary potassium wasting) and hypocalcaemia (due both to lower parathyroid hormone scores and end-organ resistance to its effect). After only magnesium repletion all abnormalities resolved, his symptoms improved. It was shown association between hypomagnesaemia and hypocalcaemia, hypokalaemia, hyperglycemia. A causal relation with PPI use was supported by the recurrence of hypomagnesae-mia after re-challenge.

Conclusion

GERD patients using PPI should have their magnesium, calcium and sodium serum levels measured periodically, and non-specific symptoms such as asthma, paresthesia or life-threatening manifestations (seizures, arrhythmias) should not be neglected.

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Utility of 11C-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. 11C-Methionine or 18F-Fluorocholine PET/CT has the potential of providing accurate and specific localization of parathyroid lesions.

Case report

We present a case of a 55-year-old woman with long-lasting history of recurrent nephrolithiasis, and osteopenia, who was diagnosed with primary hyperparathyroidism. PET/CT was then performed (04/2016), and revealed the parathyroid adenoma (9 mm in size) uptake of the tracer behind the lower part of the right thyroid lobe. Sestamibi parathyroid scintigraphy for adequate localization of the adenoma, followed by surgical removal. Based on the DXA score, we decided to initiate antosteoporotic 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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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 non-toxic 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 adenoma, 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, mild 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 9x6x3, 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. Surprisingly, despite its dimensions, this giant parathyroid adenoma did not cause severe hypercalcemia 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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P270

Multiple brown tumors in primary hyperparathyroidism caused 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 complaints 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 9–60 pg/ml). On neck examination 3 cm movable mass was palpable in the left upper neck, with high corrected calcium. Intact PTH and high calcium diagnosis of primary hyperparathyroidism was made with the doubt whether it’s a palpable parathyroid adenoma with bone metastasis. 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. 4x3x3 cm lesion was found adherent to thyroid. Therefore en bloc excision was done with hemithyroidectomy. After resection, the patient’s serum levels of calcium, alkaline phosphatase, and intact-PTH normalized Post-excision was done with hemithyroidectomy. After resection, the patient's serum calcium levels normalized. 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.

Conclusion
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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P269

Concomitant primary hyperparathyroidism with papillary thyroid carcinoma: The role of dual-phase 99mTc-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 99mTc-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 99mTc-O4 thyroid scan described no uptake of radiopharmaceutical in the left upper thyroid lobe. The 99mTc-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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P271
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 primary hyperparathyroidism (PHPT). Mediastinal ectopic parathyroid adenomas constitute about 1–3% of the cases. Brown tumors occur in less than 2% of the patients with PHPT. Moreover, those skeletal manifestations are even rarely demonstrated with maxillofacial bones involvement.

Case presentation
Here we report a 36-year-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 hyperparathyroidism (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 (0.9–0.95), ALP = 401 U/L (35–105), 24 h urinary Ca = 450 mg/24h (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, coxi and vertebra were detected. Multidetector CT scan identified multiple expansive lesions from 10×9.3 mm to 30×26 mm in frontal bone, hard palate, maxillary sinus and mandible. Cervical sonography was imagination reveals no lesion.

Conclusion
In Brown tumors and some of them did not even detected. 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 localization of PHPT, ectopic locations should also be evaluated if neck imagination reveals no lesion.

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P272
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 hypercalcemia. 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, 45 XY karyotype and testes of normal volume. Lumbar bone mineral density was increased. TSH was just over the 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 gonadotropin. 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.

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P273
Hypercalcemia not mediated by PTH: a case report
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Introduction
Hypercalcemia is a frequent hypercalcemic disorder, and primary hyperparathyroidism is the most common cause in outpatients. It is important to make an early diagnosis and adequate treatment in order to avoid possible complications such as nephrocalcinosis, 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 supravcavicular, 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), 1,25-dihydroxyvitamin D: 12.76 mg/dl (8.6–10.2), 24 h urinary Ca: 450 mg/24h (100–300), 24 h urinary Ca: 450 mg/24h (100–300), B2microglobulin: 11.06 mcg/ml (0.80–2.34), Leukocytes: 7750/10^3/μl (4.50–11.00), Erythrocyte sedimentation rate: 30 mm (1–20).

Conclusion
Sarcoidosis is a very common disorder and the majority of the patients have no symptoms. A long list of different organ involvement may be present. We describe a patient with sarcoidosis and hypercalcemia with no hyperparathyroidism.

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Endocrine Disruptors

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 5.7±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 PHPT 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 pathogenic mechanism needs more investigational research.

Keywords: Hyperparathyroidism, Tumour necrosis factor, Interleukin-6, Hypercalcemia, Auto-immunity, Leptin

Endocrine Tumours and Neoplasia

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 tumours, 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=28), 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:

<table>
<thead>
<tr>
<th>Receptors with statistical significance and their relative expression in the tumor groups</th>
<th>PA</th>
<th>APA</th>
<th>PC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear SSTR1</td>
<td>1.5%</td>
<td>15%</td>
<td>41%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cytoplasmic SSTR4</td>
<td>29%</td>
<td>40%</td>
<td>56%</td>
<td>0.027</td>
</tr>
<tr>
<td>Nuclear SSTR4</td>
<td>31%</td>
<td>51%</td>
<td>62%</td>
<td>0.008</td>
</tr>
<tr>
<td>Nuclear SSTR5</td>
<td>15%</td>
<td>51%</td>
<td>69%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cytoplasmic SSTR5</td>
<td>85%</td>
<td>78%</td>
<td>56%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Expression of nuclear SSTR5 was related to decreased parafibromin expression (P=0.002). Serum calcium and parathyroid hormone concentrations correlated with expression of 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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Female Reproduction
P279
Feasibility and efficacy in ultrasound guided percutaneous microwave ablation of primary hyperparathyroidism with parathyroid nodules
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Purpose
To investigate the feasibility and efficacy of US-guided microwave ablation on primary hyperparathyroidism patients who were excluded from surgical treatment.

Methods and materials
From May 2014 to December 2017, 30 parathyroid nodules of 25 patients underwent percutaneous ultrasound-guided MWA in our department. Contrast enhanced ultrasonography, 99Tc-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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P280
Association between age at onset of menopause and fracture risk: a systematic review and meta-analysis
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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 prostate cancer patients as compared to a control group of men within the same age group. Therefore, when administering vitamin supplementation as a method in order to keep vitamin D levels within the normal range. It should also be noted, that 25(OH)D 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.

Aim
To investigate the feasibility and efficacy of US-guided microwave ablation on primary hyperparathyroidism patients who were excluded from surgical treatment.

Methods
From May 2014 to December 2017, 30 parathyroid nodules of 25 patients underwent percutaneous ultrasound-guided MWA in our department. Contrast enhanced ultrasonography, 99Tc-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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P278
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 prostate cancer patients as compared to a control group of men within the same age group. Therefore, when administering vitamin supplementation as a method in order to keep vitamin D levels within the normal range. It should also be noted, that 25(OH)D 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.

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)D3 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)D3 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)D3 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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Endocrine Abstracts (2018) Vol 56
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). In patients admitted to our endocrinology department between 2012 and 2017 with a clinical suspicion of hypoglycemia, the diagnosis of hypoglycemia should be established only in the order to set up the underlying cause.

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.

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 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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P283

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/m²). 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 left 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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P284

Vertebral fractures in patients with type 2 diabetes mellitus
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Objective
Type 2 Diabetes Mellitus (T2DM) is a growing problem worldwide. Its pathogenesis is related to a variety of risk factors, such as age, sex, body mass index, blood pressure, waist circumference, smoking and physical activity. Diabetes can cause alterations in bone metabolism which reduces bone mass and increases the risk of fractures. Therefore, the aim of this study was to assess the occurrence of vertebral fractures in T2DM patients.

Materials and methods
We examined 100 T2DM patients, age: 64(47–85) yrs., duration of diabetes: 11(1–32) yrs., HbA1c: 6.4(5.5–10.7)% , BMI: 26.2(21.4–33.3) kg/m². The control group consisted of 100 healthy age- and BMI-matched females. Bone mineral density (BMD) was measured with dual X-ray absorptiometry. Vertebral fractures were assessed by lateral radiographs of thoracic and lumbar spine using the SPA method.

Results
In T2DM fracture incidence was 30%, while in healthy controls it was 10%. BMD at lumbar spine and femoral neck was significantly lower in T2DM patients than in controls (P < 0.001). The prevalence of vertebral fractures was significantly higher in T2DM patients than in controls (P < 0.001). Vertebral fractures were significantly more frequent in females than in males (P < 0.001).

Conclusions
Type 2 Diabetes Mellitus is a risk factor for vertebral fractures. This result suggests that the measures to reduce bone density should be taken in T2DM patients at an early stage of the disease.

DO: 10.1530/endoabs.56.P284
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(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(3.1–11) 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, X2=7.495, 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=1.998–7.012). 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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P285
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.

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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P286
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) yrs., HbA1c: 8.6(6.9–10.1) %, BMI: 33.2(29.3–36.8) kg/m². The control group consisted of 45 age-matched healthy women: 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: 6.3(3–10) yrs. vs controls: 5(2–8) yrs, P=0.009 respectively) was longer 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((−1.2)−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((−0.3)−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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Case report: male adult with autosomal-dominant osteopetrosis
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Background
Osteopetrosis is a rare chronic bone disease with high bone mineral density 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 non-familial forms. In adults osteopetrosis is often asymptomatic with increased risk for bone fracture. Treatment is symptom-based (e.g. calcium, calcichelacifero, calcitrol, 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 computed tomography 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 isoenzyme of creatine kinase (CK-BB): 0.77 µkat/l (0.0 in healthy persons); bone mineral density (in g/cm²): L1–L4 2.981; right femur 2.509; left femur 2.585 and T-score in DXA-scan (L1-L4+147; 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 computed tomography 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 differential, lactate dehydrogenase, serum calcium, intact parathyroid hormone, phosphorus, creatinine, 25-hydroxyvitamin D were not seen. Clinical controls and differential, lactate dehydrogenase, serum calcium, intact parathyroid hormone, phosphorus, creatinine, 25-hydroxyvitamin D were not seen. Clinical controls and differential, lactate dehydrogenase, serum calcium, intact parathyroid hormone, phosphorus, creatinine, 25-hydroxyvitamin D were not seen. Clinical controls and differential, lactate dehydrogenase, serum calcium, intact parathyroid hormone, phosphorus, creatinine, 25-hydroxyvitamin D were not seen. Clinical controls and differential, lactate dehydrogenase, serum calcium, intact parathyroid hormone, phosphorus, creatinine, 25-hydroxyvitamin D were not seen.

Conclusions
We established the patient’s diagnosis ADO biochemically and genetically after consultation of an endocrinologist in 10/2017. We clarified the patient of an increased risk of spontaneous and traumatic bone fracture with risky sports.

Case report: male adult with autosomal-dominant osteopetrosis
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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 obtained 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; HF: 2.2–2.7 vs 0.7–1.2 P = 0.009) and QFracture score (MOF: 8.9–6.8 vs 4.9–3.8 P = 0.012; HF: 4.6–4.8 vs 2.1–2.3 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).

Conclusions
Frailty 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/m²) 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 prevalence 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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A negative correlation was observed between 25(OH)D3 levels and BMI, a negative indicator of the inflammatory environment which characterizes 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)D3 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)D3 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)D3 levels and BMI, standardized beta coefficient = −0.87, P < 0.001. A negative correlation was also observed between 25(OH)D3 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)D3 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.

Cardiovascular Endocrinology and Lipid Metabolism

P292
Effects of atorvastatin and ezetimibe therapy on LDL cholesterol. A systematic review and meta-analysis of randomized controlled trials

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 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. Atorvastatin/ezetimibe 10/10 mg and 20/10 mg compared with atorvastatin 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 = 0.06, I2 = 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).
**P293**

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 Q10 (50 mg) in patients with self-reported statin intolerance. Secondary: effects on anthropometric (BMI, SBP, DBP, HR) and laboratory (lipids, fasting glucose and HbA1c) 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 myositis 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 analyses 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 >3×ULN. RCVE: 12.4% ± 9.3% (-25%, P=0.0071). LDL-cholesterol (mg/dL): 166.3±31.2→131.4±22.7 (-21%, P<0.0001), Total cholesterol (mg/dL): 248.6±48.4→212.3±39.2 (-15%, P=0.0077), HDL-cholesterol (mg/dL): 41.4±8.3→43.1±9.2, Triglycerides (mg/dL): 204.5±69.8→188.0±73.1 AST (UL): 39.7±11.7→33.9±9.7 ALT (UL): 56.4±6.8→32.7±9.2 GGT (UL): 67.4±18.7→63.4±17.6 CK (UL): 87.4±16.8→88.3±15.7 BMI (kg/m²): 29.6±5.2→28.9±4.7 SBP (mmHg): 144±11→141±10 DBP (mmHg): 83±9→80±7 FRP (lpm): 78±6→77±8 Fasting glucose (mg/dL) in diabetic patients: 139±21→132±17 HbA1c (%) in diabetic patients: 7.3±1.2→6.9±1.0 CKD-EPI eGFR (ml/min/1.73m²): 68.5±11.3→69.7±11.0

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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**P294**

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 sensor, 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 steatohatosis, 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 steatohatasis 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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**P295**


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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 H-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 = 0.04) and the number of CVR factors (r = 0.38, P = 0.001). 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) × 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, WHR, 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. n=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 WHR 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 WHR 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 to two groups defined by WHR index (respectively 1413.1 vs 1512.2, P = 0.4598). Concerning glucose metabolism parameters there was no correlation observed between adropin level and relation to fasting glucose and fasting insulin (rP = 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 enlargment 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-keoxin 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 PCSK9 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 χ² 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% (χ² = 31.3, P = 0.0000), exercise 25% to 50% (χ² = 22.6, P = 0.0000), pharmacological use 41.1% to 48.5% (χ² = 3.98, P = 0.04), prevention of complications 12.1% to 24.4% (χ² = 4.99, P = 0.02) and social support 13% to 26% (χ² = 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 RPC 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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P302
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/HCV co-infected population.

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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±37.2 mg/dl; P = 0.08). tryglicerides levels (114 (83.2–198.2) vs 120 (93–185) mg/dl; P = 0.37), systolic blood pressure (121 (113.2–130) vs 120 (107–130) mm Hg; P = 0.20) or diastolic 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. 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 (5.7/100000 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/kexin type 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/m2). 62.5% heterozygous familial hypercholesterolemia, 58% onset cardiovascular disease, 21% both. At baseline 66% patients were taking combination ezetimibe-statin therapy (21% rosuvastatin 20 mg/d, 4% rosvastatin 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 4–61% 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 hypertransaminemia, 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/m²). 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 reached either at fasting or 2 h after ingestion of glucose during oral glucose tolerance test. Also, there was no elevation of glycated hemoglobin 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 artery. Insulin levels at fasting were 19.1 ± 1.16, 24.1 ± 2.28, 25.0 ± 1.64 μIU/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
Hyperinsulinaemia 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 hyperinsulinaemia can play a role in the progression of atherosclerosis of coronary arteries.

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P307

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, xanthelemsas 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, echocardiogram 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.Ser19Thr (c.56 C > G) which is suggested for an increasing 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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P308
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-gluamyl 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. R² = 0.124, β = 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.

P309
Comparison of inflammatory 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, inflammatory 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 different 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. Anthropometric 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/m². 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 ± 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/b-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 HGO, abnormal HGO).

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 ±40.8% in triglycerides levels (P=0.002), of 15.4 ±14.9% in total cholesterol (P=0.001) and of 14 ±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 insulin resistance. 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 hypercorticism in 57 patients, acromegaly in 38 patients, pheochromocytoma in 27 patients and hyperthyroidism in 39 patients. General diabetes prevalence was 44%. Concerning etiology, diabetes prevalence of acromegaly was 34%, for hypercorticism (63%), for hyperthyroidism (33.3%) and for pheochromocytoma (38%). The prevalence of IBC 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 insulin therapy (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 adipoproteins 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, nephropastic 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/m², 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/m², WC 92.24 ±14.7 cm, 59.7% female. Patients with MS presented significantly elevated levels of triglycerides (200.68 ±229.5 vs 98.14 ±46.6 P<0.001) and ApoCIII (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 (X²=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. ApoCII 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/m². 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.

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 cholesterol < 40 mg/dL in males and < 50 mg/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/m², mean WC 108.6 ± 8.7 cm, 50% female. 88.1% (n = 74) were classified as metabolic unhealthy obese individuals. These patients presented a significantly increased 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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Case report

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 pharmaconkinetic 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, lixinapt 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/m². Laboratory findings were as follows: HbA1c: 10.3%; c-peptide: 0.07 µg/L. Hb: 9.2 g/dL, 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 U300, 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

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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 (33.4 ± 5.8 in T2 and 33.5 ± 6.3 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 / m² /+ /- 5 in T2 and 28 kg / m² /+ /- 3.3 in T3). on average 10.7 years (7.2 years /+ /- 5.4 in T2 and 6.6 years /+ /- 4.6 in T3) with an average HbA1C of 9.1% /+ /- 1 in T2 and 8% /+ /- 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 1.03 g / 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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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, ßCO3: 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.

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 with Graves disease who had hyperthyroidism despite high dose antithyroid medication. She applied with diabetic ketoacidosis and acute appendicitis. Respiratory arrest developed and she was intubated. Hydration, electrolyte replacement, bicarbonate replacement and intravenous insulin started due to diabetic ketoacidosis. Surgical treatment was planned for acute appendicitis. Potassium iodide, anti-thyroid theraapy and beta-blocker was started. Appendectomy was performed under spinal anesthesia after diabetic ketoacidosis had partially improved. Post-operative propylthiouracil 200 mg/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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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 uIU/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 insulin. However, patient’s relatives denied the use of exogenous insulin. 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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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 15 years due to hypertension and end-stage kidney disease. She was amnric for one year. The last dialysis session was performed 3 days ago. Her family said that 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/mm3 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 (HCO3-) 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 HCO3- 13.8 mmol/L). Then, despite the dialysis treatment, acidosis deepened (pH 6.8, HCO3- 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-performance 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-hydroxyl- glycated HbA0 may cause analytical interference in determinations of HbA1c.

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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 Cape town (α2 92Glu [E2], 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 Bancok (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 physical), obtaining 12%. Our patient was started on treatment with Efavirenz, Tenofovir and Emtricitabine (HIV therapy). Fasting glycemia 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 cell volume = 5.89 million/mm³ [reference interval (RI) = 4.5-6.4 million/mm³]; 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 wore 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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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, who sought 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): androgenc-anabolic steroids – testosterone cypionate 500 mg/wk, trenbolone 100 mg every other day, stanozolol 40 mg id, boldenone 1200 mg/wk, susostanon® 280 mg twice weekly, testosteron etanate 250 mg id, drostanolone propionate 100 mg every other day, mesterolone 25 mg 4-id, 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, lithotriyne 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 (BMI) 27.6 kg/m² 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 (0.36–1.09)), 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/m² 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 g/l (20–275)) with normalization 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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Dapagliflozin and Atkins Diet in a patient with type 2 Diabetes Mellitus: A combination that should be avoided

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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 in 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 EU/mL (normal range 0–1), anti IAA 0.05 U/mL (0–1), anti-insulin 4.5% (<6.4), with enough insulin secretion (C-peptide before eating 1.49 mmol/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/m² 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 g/l (20–275)) with normalization 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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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-anti diabetic 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 amnesia, nausea and vomit tendency over the last 24 hours. He had a previous history of hypertension, diagnosed 15 years ago and 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 l-hydroxybutyric acid and urinary ketones in the urine analysis. The diagnosis of euglycemic diabetic ketoadosis (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 ketoadosis 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 lipic acid

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Insulin autoimmune syndrome (IAS) is a rare cause of hypoglycaemia and characterized with autoantibodies to insulin in a patient without prior exposure to exogenous insulin. Medications with sulfhydryl 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 insulin autoimmune syndrome possibly caused by 2-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 hypothyroidism and hyperlipidaemia for ten years and treated with indapamin, 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 taking multivitamin preparation which contained 2-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 μU/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 hypoglycaemia 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 were 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 carbohydrate and frequent small meals was planned. Her symptoms resolved and no hypoglycaemic event was recorded. Insulin levels have decreased from 1890 μU/ml to 76 μU/ml (normal: 1.9-23) during follow-up. In all hyperinsulinaemic hypoglycemic cases, especially in patients taking medications known to be associated with the syndrome and having very high insulin levels, the diagnosis of insulin autoimmune 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 hiradenitis 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)D3 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 hiradenitis suppurativa, which, being an autoimmune disorder, may have been partially induced by vitamin D deficiency.

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Diabetes and bulimia—a dangerous combination

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A rare case of hyperinsulinemia and bulimia in a 20 year old girl who developed morbid obesity and postoperatively developed severe vitamin D deficiency.

A 20 year old girl was admitted to our clinic due to severe gastrointestinal problems and concomitant disturbances in her laboratory values. She had undergone 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 hiradenitis 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)D3 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 hiradenitis suppurativa, which, being an autoimmune disorder, may have been partially induced by vitamin D deficiency.

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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 (GI 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 30.26 kg/m², distended abdomen due to fat tissue with multiple surgical scars, psoriatic lesion on the neck. Labs exams revealed: GI=304 mg/dl, hypertriglyceridemia, low calcium and magnesium levels, glycospuria 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 Fluxetinine 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 z-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.

P328

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 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

Case presentation

A 57-year-old 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/m², 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: GI=173 mg/dl, A1c=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 Ketoprofen 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.

P329

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 glycemic 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 concentration distribute 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 inversely associated with BW z-score (P=0.81), 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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P330

Association of RS170806 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 rs1708067 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 rs1708067 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 rs1708067 genotypes, with lower concentrations of both variables on allele A carriers. We found an inverse association of the A allele of rs1718067 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 rs1718067 genotype. This project 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).

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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P332

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 stay of patients with diabetes
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Aim
The aim of this study was to identify priority roles. Logistic regression models determined characteristics associated with current practice.
P335
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 7 like 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 rs12255372(G>T) polymorphism in TCF7L2 gene was performed by real time PCR. RESULTS: There was statistically significant association between TCF7L2 gene polymorphism rs12255372 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 ethnic 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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P336
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 normoglycemics. 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 normoglycemics, 18.8% (59) prediabetics and 6.4% (20) diabetics. Data for 84 patients were available toosarah calculate HOMA-2 parameters. Mean serum zinc was found to be lower in prediabetics than normoglycemics (14.68±3.05 vs 14.96±4.01 μMol/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) and 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 normoglycemics. 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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P337
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 range 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, A. 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 IAG, average <15, 15 ≤IAG, high ≥30 IAG≥30.

Results
According to the results, low degree of OSA-I1 (27%) in women, an average severity of OSA-I2 (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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P338
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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P339
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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 (2.51) 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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P340
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 of patients with diabetes without GI symptoms ranged from 50 (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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P341
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 (DM1) 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), with the use of the Hospital Anxiety and Depression Scale (HADS), there were detected glycated hemoglobin level (HbA1C), 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 homeostasis 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 homeostasis (b = 0,64) (Exp (b) = 1,07; 95% CI – 0,99–1,15; P = 0,08).

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P342
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 FINDRASS 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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P343
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 hospital 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
Described 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-requireing 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

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P344
Evaluation of procalctonin levels in diabetic and diabetic nephropathic patients
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Aim
To determine how serum procalctonin (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), procalctonin, white blood cell, neutrophil, HbA1c and uric acid 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 nephropathic patients. However, there was a negative correlation between PCT level and eGFR.

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P345
Telmisartan increases gluconeogenesis by inducing PKC-Thr410 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)-Ser632 phosphorylation and decreased IRS-1-Tyr612 phosphorylation, indicating that telmisartan impairs insulin action in HepG2 cells. Because protein kinase C (PKC) is reported to reduce insulin action by inducing IRS-1 serine phosphorylations, we assessed its phosphorylation and found that telmisartan dose-dependently increased PKCζ-Thr410 phosphorylation. Ectopic expression of dominant-negative PKCζ constructs significantly attenuated the telmisartan-induced gluconeogenesis and the telmisartan-induced IRS-1-Ser632 phosphorylation and -inhibited IRS-1-Tyr612 phosphorylation, although it did not alter PECCK expression, showing that gluconeogenesis, when insulin is acutely treated, is largely regulated by changes of IRS-1 phosphorylations. Among ARBs, including losartan and fimepranil, only telmisartan increased IRS-1-Ser632 phosphorylation and decreased IRS-1-Tyr612 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-Thr410 and IRS-1-Tyr632 phosphorylations, respectively. Taken together, our findings suggest that telmisartan increases gluconeogenesis by inducing PKCζ-Thr410 phosphorylation that leads to increased phosphorylation of IRS-1-Ser632 and decreased phosphorylation of IRS-1-Tyr612, and consequently impairs insulin action in hepatocytes.

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P346
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 diabetes in newfoundland and labrador (NL) for any 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 (±15); 50% were women. Majority of the patients (65%) belonged to rural 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 diagnosis 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 colonenysencing factor) is an 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.

Visfatin levels in the group of healthy men (n = 10) and women (n = 10) were 0.85 ± 0.15 ng/ml (0.4–5.6 ng/ml); fasting insulin 6.7 ± 5.9 μU/ml (5.5–9.1 μU/ml); fasting glucose 88 ± 54 mg/dl (84–93 mg/dl). There were no correlation observed among differences in visfatin concentration (0.7 vs 0.8 versus 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.

Methods
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).

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 = 0.052 and P = 0.002). Serum levels of s-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 ± 0.74 ng/ml) with (F = 1.033 and P = 0.005).

Conclusions
Elderly diabetic patients with mild cognitive impairment, have higher levels of soluble adhesion molecules and markers of low-grade systemic inflammation other groups. Inflammatory mediators play a role in the development of mild cognitive impairment in diabetic elderly patients.

Keywords: Diabetics 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 65.2%, OR = 3.26, 95% CI: 2.05–5.19, P < 0.001). No significant 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
P350
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 = 0.001) compared to the IL-1β control-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-1β control-cells in HC (ALOX-5 calcitriol: 1696 ± 1004; P = 0.02) and in T2D (ALOX-5 calcitriol: 2744 ± 1372; P = 9.1 × 10⁻⁹). By comparing HC and 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 S1PR1 were significantly reduced in both HC (S1PR1 calcitriol: 575 ± 25, P = 10⁻⁵) and T2D (S1PR1 calcitriol: 5.96 ± 36, P = 0.001) compared to the IL-1β control-cells. Interestingly, T2D patients mRNA levels of S1PR2 of IL-1β control-cells compared to HC were significantly higher (P = 0.03). Calcitriol treatment did not change the mRNA levels of S1PR1 by comparing HC vs. T2D. No significant changes of the S1PR1 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 S1PR1, but on S1PR2 mRNA expression. Although calcitriol reduced the gene expression of S1PR2, 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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P351
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-phosphate 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 10⁻⁶ M calcitriol. Interleukin-1β as an inflammatory stimulant served as IL-1β control-cells. CD14, ALOX-5, S1PR1, and S1PR2 mRNA expression levels were measured by TaqMan analyses. 18s rRNA served as a house keeping gene. Gene expressions were defined as 2⁻ΔΔCt (target Ct (18sRvRNA)). 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-1β control-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-1β control-cells in HC (ALOX-5 calcitriol: 1696 ± 1004; P = 0.02) and in T2D (ALOX-5 calcitriol: 2744 ± 1372; P = 9.1 × 10⁻⁹). By comparing HC and 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 S1PR1 were significantly reduced in both HC (S1PR1 calcitriol: 575 ± 25, P = 10⁻⁵) and T2D (S1PR1 calcitriol: 5.96 ± 36, P = 0.001) compared to the IL-1β control-cells. Interestingly, T2D patients mRNA levels of S1PR2 of IL-1β control-cells compared to HC were significantly higher (P = 0.03). Calcitriol treatment did not change the mRNA levels of S1PR1 by comparing HC vs. T2D. No significant changes of the S1PR1 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 S1PR1, but on S1PR2 mRNA expression. Although calcitriol reduced the gene expression of S1PR2, 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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P352
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 adipocytokine 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 specifically 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 glycometric 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 glycometric 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 working subjects 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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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.

**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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**P354**

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 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 (±1.59) ng/mL in all patients, 0.96 (±3.03) in group 1, and 3.11 (±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 ≥30kg/m2), diabetes duration, use of secondogine, diabetic ketoacidosis history, HbA1c (<10 or ≥10%), hyperlipidemia or hypertyglicycedemia, 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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**P355**

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 ≥ 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 ≥ 1 capillary blood glucose ≥ 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 nondiabetic 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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**P356**

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
P357 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 calculation in Korea.

*The data includes multiple counting among clinical departments.

Table 1 Annual numbers of patients.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Patients</th>
<th>New Patients</th>
<th>Claimed Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>20,330</td>
<td>16,854</td>
<td>3,476</td>
</tr>
<tr>
<td>2012</td>
<td>18,143</td>
<td>14,475</td>
<td>3,668</td>
</tr>
<tr>
<td>2013</td>
<td>18,371</td>
<td>14,290</td>
<td>4,081</td>
</tr>
<tr>
<td>2014</td>
<td>18,047</td>
<td>13,767</td>
<td>4,280</td>
</tr>
<tr>
<td>2015</td>
<td>17,549</td>
<td>13,357</td>
<td>4,192</td>
</tr>
<tr>
<td>2016</td>
<td>16,613</td>
<td>12,365</td>
<td>4,248</td>
</tr>
</tbody>
</table>

P358 Think insulin: a prospective study of the knowledge of insulin preparations and administration in a Cohort of nurses in district general hospital
Emma Jade Shepherd, Surya Ashutosh, Sian Jones, Julie Jones, Beth Mumford, Gaynor Harrison & Hussam Abusahmin
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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 other colleagues 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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P359
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 Neutrometer). 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 neutrometer 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.

Objectives
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 glycated haemoglobin (Hba1c) at onset of diabetes.

Results
We analyzed data from 69 patients with mean age 26 (±10.8 years), 61% males; IMC 23.6 ± 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-lgA2 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 ± 0.9 mg/mL and insulin values 5 ± 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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Virgen de la Victoria Hospital, Málaga, Spain.

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) that is considered positive if at least two or more values ≥ are ≥ of reference values (105-190-165-145 mg/dl). Despite it is not included 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 100-g 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 (5.9%) 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.

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 reduced to be 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 GM1, 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 GM2 at 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 sphingomyelinas, 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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1Cruces University Hospital, Barakaldo, Spain; 2BioCruces Health Research Institute, Barakaldo, Spain.

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 (59.5% 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, glycaemia, HbA1c, BMI, pancreatic autoantibodies GAD, IAA2 and IAA (measured by radioimmunossay 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: Preliminary Analysis). Results
26.7% of patients had ketoacidosis at onset. Median glycaemia at diagnosis was 359 mg/dL (IQR 150), being mean HbA1c 11.95% (SD 2.52) and median BMI 22.48 kg/m² (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).

<table>
<thead>
<tr>
<th>Number of HLA risk alleles</th>
<th>Under 15 years</th>
<th>Over 15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Alleles</td>
<td>1 Allele</td>
<td>2 Alleles</td>
</tr>
<tr>
<td>Under 15 years</td>
<td>12 (7.5%)</td>
<td>71 (44.4%)</td>
</tr>
<tr>
<td>Over 15 years</td>
<td>55 (20.0%)</td>
<td>119 (43.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>67 (15.4%)</td>
<td>190 (43.7%)</td>
</tr>
</tbody>
</table>

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P365

Lipodystrophic Diabetes Mellitus: a rare special type!
Shaimaa A Fathy, Asem Seif, Heba Sherif & Dina Farouk
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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), impaired coagulation profile (INR: 1.2; n: 1) and hypoplasminemia (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 except LDL of 62 mg/dl (n> 70 mg/dl). Liver and kidney function tests, hepatits markers and autoimmune hepatitis markers were normal. Her TSH was normal, but her FSH was 1.0 IU/ml (n: 1.5–9 IU/ml), LH: 0.2 IU/ml (n: 1–11.4 IU/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 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 Thiouzolides and Metformin can improve insulin resistance in the early disease before the onset of liver cirrhosis. Later on in liver and lepithin remain the only treatment lines.

Key words: Lipodystrophy, Insulin resistance, Diabetes Mellitus, fatty liver, liver cirrhosis.

References

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P366

Does gender-affirming hormone therapy after insulin resistance in transgender persons?
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*Both authors contributed equally to this work.

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). HOME-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 HOME-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 HOME-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 HOME-IR and a positive correlation (R = 0.287, P = 0.034) between change in HOME-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 score.

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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 rRNA [G] gene. The clinical characteristics normally associated with this disease include sensorineural hearing loss, macular 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 was 23.5 (± 3.2)kg/m². 16 (82%)patients were misidentified as Type 1 Diabetes 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>T mutation. Heteroplasmy was determined in 24 patients (69%) 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)/2.13 (± 7.7), 63.3 (± 25.3)/0.707 (± 0.013) and 570.6 (± 201.4)/0.2187 (± 122.48). 31 (93.9%) patients had Hba1c with mean of 6.6± (± 18.6) mmol/mol. 13(39%) patients had metformin discontinued. 14(42.4%) patients are on insulin alone. 5(15.7%) 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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Eaplibicen Scientific Center for Radiation Medicine and Human Ecology, Gomel, Belarus.

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) = 1.08 (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 (OR – 10.14 (1.27 – 0.8); Exp(b) = 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 (T) 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 T propionate and T 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’ ophthalmopathy (GO), the diagnosis was based on clinical activity score (CAS), TSH-receptor antibodies, orbital MRI assessment. Thyrometabolic 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 from the study. The aggregation of severe metabolic disturbances in DM patients treated with systemic corticosteroid therapy (especially glucocorticoids). As a result, insulin treatment 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 performed routinely in patients with GO before systemic corticosteroid therapy.
3. Acute hyperglycaemia is observed in patients 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 who 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.

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samples for plasma c-peptide, insulin and cortisol level measurement were obtained. Her plasma c-peptide was 3 mmol/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 deficiency. The patient’s urine ketone was negative during this period. Urinary sulfonflies metabolites were unmeasured because of laboratory inability for the patient who has endogenous hyperinsulinemia and hypoglycemia at the same time. A sudden spontaneous hyperglycemia 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 initiated to control blood sugar levels. During that stage HbA1c and anti-insulin autoantibodies 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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P373

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 bronchietasis 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 BMl was 22.4 kg/m² 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 functions 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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P375

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 influence 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), polysonographic study “SOMNO-lab2, Weimann 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 - 5.0–6.50 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 glycemia 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 (2.10 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 decompensation (HbA1c 8.95%) improves the structural parameters of sleep: reduces REM stage, 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.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Before correction of insulin therapy Me[25;75]</th>
<th>After correction of insulin therapy Me[25;75]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>8.95 [7.50;9.30]</td>
<td>8.95 [7.50;9.30]</td>
</tr>
<tr>
<td>The minimum glucose level during sleep (mmol/l)</td>
<td>8.20 [7.50;9.50]</td>
<td>5.50 [5.50;6.50]</td>
</tr>
<tr>
<td>The maximum glucose level during sleep (mmol/l)</td>
<td>13.80 [10.50;15.00]</td>
<td>6.50 [6.00;7.00]</td>
</tr>
<tr>
<td>Sleep Efficiency Ratio (%)</td>
<td>70.00 [69.00;73.00]</td>
<td>86.70 [84.90;87.00]</td>
</tr>
<tr>
<td>WASO (wake after sleep onset)(min)</td>
<td>71.00 [35.00;94.00]</td>
<td>31.00 [25.00;47.00]</td>
</tr>
<tr>
<td>REM (%)</td>
<td>39.90 [36.70;41.40]</td>
<td>35.37 [24.51;37.10]</td>
</tr>
<tr>
<td>N3 (%)</td>
<td>2.8 [0.00;4.28]</td>
<td>5.10 [3.81;6.40]</td>
</tr>
<tr>
<td>N4 (%)</td>
<td>1.20 [0.00;4.20]</td>
<td>3.70 [2.50;4.80]</td>
</tr>
</tbody>
</table>

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 an impaired 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-%β < 100% in comparison to the 36.4% of patients with normal glucose tolerance which had an HOMA-%β < 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 significant.

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 probes 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 mutation (M_000458_2:c.884G>A (p.R295H)) in the DNA-binding homeodomain of the HNF-1β 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 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**


**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 (HbA1c 7.6 ± 0.9%; Age 28 ± 5 years; BMI 23.7 ± 1.8 kg/m2; 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 ≥ 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 ± 68.2 g 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-α 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 methods
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-g 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-1 (HNF1) b Mutations
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Background
HNF1b mutations are one of the commonly identified genetic causes of renal malformations, but one of the less common forms of MODY. HNF1b 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 HNF1b variants and the challenge of management on the basis of the insulin secretory response to glucose.

Methods
11 HNF1b 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/m2, 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 HNF1b mutation positive, with a significant reduction of insulin doses. 29/ on OHAs required basal insulin after 10 years of diabetes diagnosis, 1/9 on OHAs 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/20 min: 9.3±4.8/19.3±8.3, 56.2±65.8/150.0±77.3, 363.7±219.5/1364.0±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 HNF1b 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 OHAs 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/m2 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 ± 9.92 years; the mean BMI was 34.39 ± 6.72 kg/m². 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 (54.3%) 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 scored on a Likert scale from 0 (never, seldom, or sometimes) to 3 (always). The 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 – ‘sometimes’. 20 – in 13 ones (65%). In the subgroup of women 42 females (48.7%) were scored on a Likert scale from 0 (never, seldom, or sometimes) to 3 (always). The 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 – ‘sometimes’. The higher score was in the subgroup of women 42 females (48.7%) were scored on a Likert scale from 0 (never, seldom, or sometimes) to 3 (always). The 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 – ‘sometimes’.

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 Karoliniškio 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 30.1±2.513 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 overweight and normal weight women group than that in overweight and obese women group (13.87 ± 4.85 vs 11.59 ± 5.88 kg (P = 0.0001)). Mean total GWG was higher in normal glucose tolerance group compared to GDM group (13.73 ± 4.84 vs 12.15 ± 6.09 kg). 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 delivery 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 5% (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 ± 55.0 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 ± 8.5 weeks; 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; IC95% 1.50–11.40), newborn large for gestational age (LGA) (OR = 3.29; 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 ≥ 35 years (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 reinforce 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 (25(OH)D) 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 Cecillo 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 (25(OH)D, intracatabolized osteocalcin [iSoC]) 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/m², 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.; 25(OH)D 42.9 ± 19.8 ng/dl; HbA1c 5.4 ± 0.3%; uOC 8.3 ± 10 ng/ml. Circulating levels of 25OHOD 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 uOC. The patients with serum 25OHOD ≥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 25OHOD 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.

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 profiles 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 according 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 kg²/m² 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 vs 115.97). 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 glycerides and 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.

Objectives
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 concentration of glutathione (GSH) 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 GSH and GSH were significantly lower, compared with group 3 (p₄₋₃ = 0.012, p₄₋₁ = 0.053, respectively). When compared with the group group 4, a significantly higher GSH content was detected (p₄₋₄ = 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 (p₄₋₂ = 0.006, p₄₋₃ = 0.006, p₄₋₅ = 0.003, p₄₋₃ = 0.005, p₄₋₃ = 0.009, p₄₋₅ = 0.014, respectively, and p₄₋₃ = 0.005, p₄₋₁ = 0.016, p₄₋₁ = 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 GSH in group 4, compared to group 1 (p₄₁ = 0.004, p₄₋₁ = 0.016, respectively), and an increase GSSG (p₄₋₁ = 0.004). Eh was significantly higher in group 4 than in groups of 1,2,5, p₄₋₁ = 0.035, p₄₋₁ = 0.013, and p₄₋₁ = 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 serotonergic receptors
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Introduction
Type 1 diabetes mellitus (T1DM) is a chronic autoimmune autoimmune disease characterized by a lack of β-cell function and insulin resistance (IR). The pathogenesis of T1DM is complex and involves both genetic and environmental factors. However, the precise mechanisms underlying the development of IR in T1DM are still not fully understood. Addressing this issue is critical to the management of T1DM and improving the quality of care for patients. The aim of this study was to investigate the effect of the dopamine agonist cabergoline on insulin sensitivity in the skeletal muscle and to explore the underlying mechanisms.

Materials and methods
C2C12 myoblasts were cultured and differentiated into myotubes. The cells were treated with cabergoline (CAB) at different concentrations and time points. The expression of glucose transporter 1 (GLUT1) and the phosphorylation of extracellular signal-regulated kinase (pERK) were assessed by Western blot analysis. The percentage of glucose units (GU) was calculated using the formula: (Amount of glucose at baseline - Amount of glucose after treatment) / Amount of glucose at baseline.

Results
The treatment of C2C12 myotubes with CAB at concentrations of 10⁻⁸ M and 10⁻⁶ M led to a significant increase of % GU as well as GLUT1 membrane translocation after 8 h. 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. In conclusion, these data show that CAB induces muscle GU both at baseline and IR conditions by improving insulin and AMPK pathways, respectively.
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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 outcomes during the past 8 years in our pregestational 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). We described 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 analyzed data, evaluating differences using χ² test, Student’ t-test on Mann–Whitney test.

Results

As compared with T1DM pregnant, T2DM pregnant were older (age: 33.9 ± 4.9 vs. 31.0 ± 0.5 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: 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 1st trimester (6.5% (6.0–7.2)) were detected, but during 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%, newborn long 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 in maternally 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 neurosensory 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 neurosensory 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/m². 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. Electrolymogram 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/m²). She was referred to our center and insulin therapy was initiated as well as autoimmune study was requested. Blood test showed anti GAD level of 3701.9 U/ml (normal range: 0.3–9.1) 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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P392
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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P393
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 ‘Lidiane’. 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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P394
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 1/4 cases, with a significantly higher incidence of diabetic retinopathy 42.5% versus 8-13% in the literature. Regarding the extra-pancreatic manifestations, reticulocar mal dysmophry, very characteristic of DM, was absent in all our patients; as well as retinits 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 Glu) found in 60% of cases. A second at 12% of cases was m.11778A>G (tRNA Leu) found in 60% of cases. A third was m.3460A>G (tRNA Ser). 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 heteroplasmy 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 heteroplasmy 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 PCOS) women with T1DM (mean ± SD; age 28.7 ± 6.1yrs, BMI 25.4 ± 4.4kg/m²), and 87 (16 PCOS) non-diabetic women (mean ± SD; age 31.8 ± 5.9yrs, BMI 28.3 ± 4.01kg/m²), 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= -0.32), 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 positive(r= 0.22) with TG and TG/HDL-C ratio(r= 0.24) while androstenedione correlated positively with TCR(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=0.39, 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 non-diabetic 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 only. These results do not support a role of hyperandrogenaemia in atherosclerosis in T1DM. The role of VLDL and sdLDL in early atherosclerosis 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 hyperglycaemia 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 glycaemia. 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 (χ² = 1.13, P = 0.29 and χ² = 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 glycaemia (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 insulin, and these studies of the role of FTO polymorphism in the development of carbohydrate metabolism disorders are required.

Keywords: FTO gene, diabetes mellitus type 2, impaired glucose tolerance

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P397
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 insulinaemia 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 symtomatic 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 sweating 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-syncpe 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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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 hyper 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 Roch 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, JINDEX, HBGI, 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 (8.85 ± 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<0.010) and ADDR (30.22 ± 9.8 vs. 26.02 ± 10.5; P=0.006). We established a significant correlation between Abs anti-GAD65 (r= -0.137; P=0.031) and Ab anti-IA2 (r= 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, and cause 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 highlights the importance of improving the prevention and treatment of cardiovascular complications in this population.

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P403
Screening for autoimmune endocrinopathies: At 300 insulin-dependent diabetes type I
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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 Roch 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.

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 motivated the early morning cortisol assessment 98% of the cases, asthma in 82%, and Weight loss in 77% and the melanoderma 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 months and 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 hypothyropathies 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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P404
Diabetes complications

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 underwent 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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P405
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 (54.1%) 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 was 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 analyzed 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; surgery, could be beneficial in terms of morbidity.

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P408
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 within the last year was 48%. Most of them (45%) visited their dentist mainly when urgent treatment was needed or because of pain.

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dentist for check-up. Approximately 19% didn’t visit a dentist at least 5 years ago and 8% did not consult a dentist. The higher the HbA1c was, the more recent was the dentist visit (P=0.002). 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 21% skipped tooth brushing altogether. We observed that women were more frequent users compared to men.

Conclusion: Despite the greater risk for the development of periodontal disease, the oral self-care was poor among Tunisian diabetics. 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 is often forgotten as they actually affect the quality of life. The repercussions of this complication can influence 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 53.7 ± 10.8 years. The family history was type 2 diabetes in 78.9%, hypertension 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 48.9% of cases, oral antidiabetic alone in 8.4% 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% and diabetic nephropathy in 18.2% of cases. The mean BMI of patients was = 26 ± 5.6 kg/m² 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 ± 1.53 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 glycaemia and cognitive function in patients with type 1 diabetes mellitus
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Objective
To determine the effect of glycaemic 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 by D55 Glycogram (Drew Scientific, The Netherlands). For the diagnosis of fluctuations in glycaemia, continuous monitoring of glycaemia was conducted using the IPro-2 (Medtronic, USA) and CareLink (EnProTm) software. EasyGV calculator (2011) was used to analyze the variability of glycaemia. The following indices were studied: mean glycaemic mean (MEAN), standard deviation (S.D.), mean amplitude of glycaemic fluctuations (MAGE), long-term glycaemic index (CONGA), glycaemia liability index (LI), hypoglycaemia risk index (LBI), hyperglycaemia risk index (HBI), mean hourly rate of change in glycaemia (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 mellitus 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 ± 1.3%, and in the control group it was 6.7 ± 0.25% (t = −2.5, P = 0.015). Significant difference in MEAN, s.d., CONGA, LBI, HBI, MAGE and MAG values between the groups is recorded. When performing the correlation analysis, it was shown that the level of HbA1c (γ2 = −0.450, P = 0.014), as well as the parameters of the variability of glycaemia-MEAN (γ2 = −0.584, P = 0.001), s.d. (γ2), affects the cognitive functions in type 1 diabetes. = 0.022, P = 0.022), CONGA (γ2 = −0.853, P = 0.001), LBI (γ2 = −0.451, P = 0.014), HBI (γ2 = −0.053, P = 0.003), MAGE (γ2 = −0.480, P = 0.008), MAG (γ2 = −0.573, P = 0.001).

Conclusion
In patients with type 1 diabetes mellitus, hyperglycaemia and hypoglycaemia, the duration of the increase in glycaemia and the average fluctuation in glycaemia 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. Systemic symptoms were 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% & 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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**P412**

**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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**P414**

**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/m². 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 (CaP) 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 CaP level were the best predictors of the occurrence of carotid plaque.

Conclusions

Our study showed that HbA1c level is associated with the CaP 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 ± 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 low 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-HypoGi 5.5±0.4, which submit middle degree of episodes of hypoglycemia in this group.

Conclusions
The using of CSP-DM-HypoGi gives possibility to evaluate the degree of symptomatic hypoglycemia in patients with DM 2
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P416
Comparative 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 patients; 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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P417
Thiol-disulphide 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-disulphide 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 classified as patients without PNP. Patients with discordant results were excluded. According to the regrouping, serum HbA1c (9.5±2.0% vs 8.9±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±29.9 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>0.02, P=0.02 and P=0.03, respectively).

Conclusions
In our study, there was no significant increase in serum TAC, AOPP, and thiol-disulphide 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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P418
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 hyperglycemic states has been proved.

Table 1 Laboratory characteristics of glycemic control and lipid metabolism.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Me (25;75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, %</td>
<td>9.00 (7.70; 10.60)</td>
</tr>
<tr>
<td>The minimum level of glucose, mmol/l</td>
<td>2.70 (2.20; 4.10)</td>
</tr>
<tr>
<td>The average level of glucose, mmol/l</td>
<td>10.10 (8.30; 12.20)</td>
</tr>
<tr>
<td>Duration of hypoglycemia, %</td>
<td>5.00 (2.00; 10.00)</td>
</tr>
<tr>
<td>Duration of hyperglycemia, %</td>
<td>9.00 (32.00; 68.00)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>4.60 (4.00; 5.20)</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>0.92 (0.68; 1.37)</td>
</tr>
<tr>
<td>HDL (high-density lipoproteins), mmol/l</td>
<td>2.08 (1.55; 2.89)</td>
</tr>
<tr>
<td>LDL (low-density lipoproteins), mmol/l</td>
<td>1.73 (1.34; 2.42)</td>
</tr>
<tr>
<td>VLDL (very low density lipoproteins), mmol/l</td>
<td>0.40 (0.30; 0.62)</td>
</tr>
<tr>
<td>Atherogenic index</td>
<td>2.10 (1.60; 2.70)</td>
</tr>
</tbody>
</table>

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P419

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 patients 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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P420

APOB/APOA1 ratio is associated with metabolic syndrome in type 2 diabetes mellitus women with ischemic cardiomyopathy

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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 referral, which provides services to the 31 urban district of Madrid, Spain (Vallecso 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 ATP III (National Cholesterol Education Program’s Adult Treatment Panel III) 2. The following variables were measured in serum or plasma samples: Cholesterol, 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, version 21.0).

Results
We found associations, that remain after adjusting comorbidities and risk factors, between MetS and ApoB/ApoA1 (R²=0.164, P=0.028), ApoB/ApoA1 ratio (R²=0.187, P=0.001); and Non-HDL-Cholesterol/HDL-Cholesterol ratio (R²=0.269, P=0.003). 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 (R²=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 seems 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±125 mg/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 (CAGs).

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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P422

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.

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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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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 from volunteers. 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 HDL3 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 antithrombogenic effects of HDL cholesterol subclasses.

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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 8.53 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, 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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The comparison of serum cerebellin and catecholamine leassins 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,
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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 was 28.1±6.2 (27.5–28.8) years, duration of the disease was 9.0 (7.0–12.0) years, body mass index was 24.8±3.95 (23.6–25.2) kg/m². 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 group (Gr2) – 103 (28.6%) people – mostly not committed to the control of glycemia. To verify the DPN the Vibration device was 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 HbA1c, 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±2.1, 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% (χ²=4.67, P=0.030), microvascular complication – 71.6 vs 83.5% (χ²=5.55, P=0.018). However, there were no differences in the prevalence groups of DN – 62.6 vs 51.5% (χ²=4.57, P=0.051), albuminuria 35.4% vs 44.7% (χ²=4.67, P=0.030), DR – 51.4% vs 54.4% (χ²=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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Inflammation in patients with diabetic nephropathy receiving different classes of glucose-lowering medications: serum levels of interferon gamma

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Proinflammatory 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 Spearman’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 (14.8±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, homoglobin, 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 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 inpatient 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 discount 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 habits, 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 evaluated eighteen of whom were outpatient, and thirty six of whom were inpatient.

Results
The majority of patients were suffering from type 2 diabetes mellitus (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 outpatient. 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.

References

Table 1 Characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Outpatient (n=18)</th>
<th>Inpatient (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male/female (%)</td>
<td>13 (72.2%)/5 (27.8%)</td>
<td>21 (58.3%)/15 (41.7%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.3 (52–78)</td>
<td>62.9 (40–80)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>21.2 (3–40)</td>
<td>19.9 (4–40)</td>
</tr>
<tr>
<td>Type 2 DM (%)</td>
<td>18 (100%)</td>
<td>33 (91.7%)</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>10.4 (6.9–14.4)</td>
<td>9.3 (6.1–14.2)</td>
</tr>
<tr>
<td>Diabetes education (%)</td>
<td>2 (11.1%)</td>
<td>15 (41.2%)</td>
</tr>
<tr>
<td>Diet compliance (%)</td>
<td>2 (11.1%)</td>
<td>8 (19.4%)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>4 (22.2%)</td>
<td>19 (52.8%)</td>
</tr>
</tbody>
</table>

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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±5.1) 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±6.7, 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, 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.

Conclusions
The results of this study provided evidence that women of reproductive age with T2DM present early atherosclerosis compared to healthy controls, but the
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Association of adverse pregnancy outcomes with glycemic cut-offs stated by the IDA-PDSG, 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 (IADPSG) 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 undergone 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 referred 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 claudiation (1.06 ± 0.18) (P = 0.003). The left ABI was found to be higher in patients with claudiation (1.11 ± 0.2) than patients without claudiation (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, dipp, glitazone or insulin use were not found to be related to 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 measurements. 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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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/m² 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 1.16 ± 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 < 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, albuminuria, hypomagnesemia.

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P436

Association 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 mm² vs. 2.71 ± 0.57 mm², 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 outcomes 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-4i 5(45%), GLP-1 agonist 3(27%) and sulfonilureas 2(18%). Mean blood glucose was 280 ± 84. Precipitating factors: 2(18%) had infection, 1(9%) drinking alcohol, 6(54%) 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, albumin, 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 $<200$mg/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.

Conclusion

**P439**

**Hyperlipidaemia 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 effect 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 dyslipidaemia 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 dyslipidaemia during pregnancy was determined using two different classifications.

Results
Lower plasma HDL and hypertriglyceridaemia were the most current disorder; prematurity or birth weight were not correlated with dyslipidaemia; 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.

**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 recurrence 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 1 than 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.

**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 $\geq 4$ 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 mol/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: 3.0 ± 1.2 vs. 3.7 ± 0.6). We did not find a difference of PAID Score in patients with and without IAH had (score 19.1 ± 1.7 vs. 18.7 ± 0.6). 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.
P442
The comparison of the fate of arteriovenous fistula in diabetic and non-diabetic recipients following kidney transplantation
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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 < 0.001; 51 ± 8 vs 44 ± 10 years, P = 0.004 and 29.2 ± 5 vs 26.9 ± 7.8 kg/m², 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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P443
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 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 11.670 yrs; duration of T1D 23.07 ± 9.95 yrs) with T1D after renal transplantation (GFR 64.0[49.00; 75.00] ml/min). In group 1–21 patients received replacement therapy with levotiroxyn, 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
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 improvement 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 our hospital between October 2016 and October 2017. We audited adherence 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.

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 respondents 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 from ICU guidelines 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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P445
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 importance 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 ± 5.4) 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, 1,5-AG 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/m², 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 ± 0.3% respectively. The number of glycemic excursions were 16.2 ± 7.3 which was consist of high (11.6 ± 6) and low excursions (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, 52.63 ± 120 nM and 0.53 ± 0.06 μM 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 = −0.469, P = 0.002). There were no significant interactions between cytokines and MAD%, glycemic excursions in CGMS.

Conclusion
Including 1,5-AG, glycemic markers do not reflect glycemic variability. CGMS can be used to assess hypoglycemia and glucose variability in conjunction with HbA1c. It is also important for treatment adjustment in all patients with type 1 diabetes and patients with type 2 diabetes treated with insulin therapy.

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P446
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 (DFS) with a healing rate of ulcerative defect and diabetes compensation.

Materials and methods
Twenty-four patients with DFS (DF5 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-1, IL-6, IL-8, IL-10, TNF-α, IL-4, IL-13, TGF-β) and oxidative stress markers (8-isoprostane, a marker of oxidative stress, and endogenous NOS inhibitor - asymmetric dimethylarginine (ADMA). 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 = −0.469, P = 0.002). There were no significant interactions between cytokines and MAD%, glycemic excursions in CGMS.

Conclusion
Including 1,5-AG, glycemic markers do not reflect glycemic variability. CGMS can be used to assess hypoglycemia and glucose variability in conjunction with HbA1c. It is also important for treatment adjustment in all patients with type 1 diabetes and patients with type 2 diabetes treated with insulin therapy.

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P447
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 complications of diabetes. The tendons and ligaments’ stiffness and elasticity are known to be altered in diabetic foot. Achilles tendon (AT) plays an important role 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 neuropathy 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).

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Control Group</th>
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<tr>
<td>SWV of right AT (m/s)</td>
<td>4.0 ± 1.1</td>
<td>5.4 ± 1.0</td>
</tr>
<tr>
<td>SWV of left AT (m/s)</td>
<td>4.0 ± 1.1</td>
<td>5.5 ± 1.1</td>
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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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P448
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/m²) (data are presented everywhere as mean ± SEM). All patients were performed coronaroventriculo-gramphy, 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 5 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 = 0.45, 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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P449
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 (T1D).

Methods
A cross-sectional study of 174 subjects with carotid atherosclerotic plaques (46.6% women; mean age 53.6 ± 10.2 years; BMI = 27.1 ± 5.8 kg/m²) were included. The data were analyzed by SPSS 24.

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. 38.4%; hyperechoic 25.2% vs. 25.9%; hypoechoic/hyperechoic 16.8% vs. 20.2%, 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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P450
Neurosensorial hearing loss in type 2 diabetic patients
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Introduction
There is a connection between neurosensorial hearing loss and type 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 which diabetes can damage the eyes and the kidneys.

Aim
The role of type 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 professions, 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 type 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 which 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 audiogramme in every patient detected with diabetes.

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P451
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.

Method
The study included 70 patients with type 2 diabetes and diabetic nephropathy (group 1; 35 patients with eGFR <30 ml/min/1.73 m²) and group 2; 35 patients with with eGFR <30 ml/min/1.73 m² 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±0.83 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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**P452**

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 therapy. It was difficult to create an AVF in diabetic patients. They 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/m², \( P<0.001 \), 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 (\( P=0.17 \), vs 60, \( P=0.220 \)).

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) phototopometry using the Perimed Laser Doppler Imager. Endothelial-mediated vasodilatation (EMV) was measured by the photothermometry of acetycholine (Ach), while sodium nitroprusside (SNP) was used to study endothelium-independent vasodilatation (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 and inflammatory 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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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-B) and the inflammatory marker IL-6. Calcanear bone mineral density (BMD) was measured using a quantitative ultrasonic 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 calcanear 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 rate 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 sclerostin 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 an 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 anti-sclerostin-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 a 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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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 stress 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 (38.58%) 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 than the other group (P=0.018). Triglyceride levels in the diabetic complication group were significantly higher than the other 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 gestational 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 ≥92 mg/dl in the first trimester or a 7g-OGTT at 24–28 weeks with at least one abnormal value (≥92; ≥180 or ≥153 mg/dl at 60, 120 or 180 minutes, 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 (≤37 weeks), neonatal hypoglycemia, neonatal hyperbilirubinemia, neonatal distress respiratory syndrome, or trauma during delivery. We compared women with and without perinatal complications: χ2 test, student t test and Mann Whitney U test.

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 ± 60.5 mg/dl vs 109.0 ± 45.8 mg/dl, P = 0.002), higher triglycerides (90.5 ± 67.8 mg/dl vs 79.0 ± 60.0 mg/dl, P = 0.002); and significantly lower HDL-cholesterol at onset (45.5 ± 22.2 mg/dl vs 49.0 ± 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 (95% CI: 1.001–1.05), P = 0.005). However, the association between HDL-cholesterol and DR in multivariate analysis was only marginally significant (HR 0.91 (95% CI: 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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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 as angiopeptin 2 (Ang2) and neuropetide 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 Lumimex 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 spectrscopy 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: 50.05±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).

Conclusions
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 (1015.2±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 mg/ml vs 14.52±5.77 mg/ml, P=0.005).

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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, immuno reactive 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.

Conclusions
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 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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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=0.178). 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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Wrist and ankle measurements in patients with and without diabetes-related macrovascular disease

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Background
Carotid and femoral territories in a large cohort of Spanish CKD patients without previous CVD.

Aim
We aimed to evaluate wrist and ankle measurements in patients with and without diabetes-related macrovascular disease.

Material and methods
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=0.000) (OR 12.533, 95% CI 4.191–37.596), statin use (P=0.018) (OR 2.426, 95% CI 1.156–5.039), metformin use (P=0.008) (OR 3.379, 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), wrist 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 study, 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 macrovascular complications as waist/hip ratio.

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Prevalence and risk factors of diabetes in chronic viral hepatitis B and C: 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 between 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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P467
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 eighty three patients who applied to Endocrinology and Metabolism and Geriatric Medicine Polyclinics 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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P468
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 ± 4.9). 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 was 0.2915 mg/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 = 1.10, 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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P469
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 ketoacidosis during 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 Shawal. 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 Shawal). 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 diabetes
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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/m²; the neurological symptoms score (NSS) – 18.1±0.2 points; HbA1C – 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 13C-octanoate breath test (13C-OBT) No subjects studied have had the signs of other disorders of dysfunction in gastrointestinal motility.

Results
Accompanying 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 = 0.56–1.19, P=0.000; whereas the 13C-OBT and the NDS RR = 2.20, 95% CI = 1.13–3.72; 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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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 FIB4-4 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 were required variables (age, AST, ALT, and platelet count) were available. Of the remaining 1043 (58.69%), 30 (2.88%, 30 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 <3.23, 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 FIB4-4 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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Accumulating facts show that incretin-modulating therapy could be beneficial in both glycemic control and nephropathy protection 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 (eGFRcre), cystatin C (eGFRcys), and both (eGFRcre-cys), and creatinine- and cystatin C-based markers (chronic kidney disease epidemiology collaboration (CKD-EPI), and cystatin C-based IV (uCoIV). 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 uCoIV was documented in Vgroup as well as the increase of eGFRcre and eGFRcre-cys. Correlation analysis showed that neither changes of serum cystatin C, eGFRcre and eGFRcre-cys nor changes of uCoIV 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 eGFRcre-cys (β=−0.47, R²=0.22, P=0.02) suggesting that hemodynamic mechanisms at least partially contribute to vildagliptin renal action. Stepwise regression analysis showed that lower levels of baseline eGFRcre were independent predictors of both eGFRcre and eGFRcre-cys increase (β=−0.61, R²=0.37, and β=−0.45, R²=0.20, respectively, P<0.05 each). Reduction of uCoIV excretion was more pronounced in older patients (β=−0.74) with lower levels of diastolic BP (β=0.57, R²=0.46, P=0.002. In conclusion, vildagliptin administration was associated with reduction of uCoIV excretion along with the increase of eGFRcre-cys and eGFRcys, independent of glycemic control. Older age and lower baseline values of uCoIV were predictive of better uCoIV- response in patients receiving vildagliptin.

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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-12.6% and GII-14.2%. 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
Plasmatric 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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P475
Bacterial lower limb dermo-hypodermitis in 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 Rochdi 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.

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.

Result
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 ≤ 0.05). 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)), diarrhoea (14.3% for dulaglutide and 11.1% for liraglutide (P = 0.83)) and decreased appetite (28.6% for dulaglutide and 33.3% for liraglutide (P = 0.09)). 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 painful rash induced by linagliptin in a patient with type 2 diabetes
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Introduction
Although dipeptidyl peptidase-4 (DPP-4) inhibitors 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 painful maculopapular rash induced by linagliptin, a widely used DPP-4 inhibitor.

Case presentation
A 54-year old female patient with newly diagnosed T2 diabetes admitted to our outpatient clinic due to nausea, vomiting, polyuria and polydipsia. Physical examination was normal except for a reduced skin turgor and tony. On biochemical analysis, her fasting plasma glucose (PGP), HbA1c, white blood cell count (WBC), serum creatinin, BUN and C-reactive protein levels were 300 mg/dL, 59.8, 17.000 (570 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 3rd 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 painful, 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 cessation of linagliptin and starting treatment with bethametasone ointment, the pain and maculopapular rash were completely disappeared.

Conclusion
The present case suggests that like other DPP-4 inhibitors such as sitagliptin and vildagliptin, linagliptin may also cause skin reactions. Therefore, attention should be paid to patient receiving this class of drugs and treatment should be stopped after appearance of skin reactions. However, it is not well known whether cross reactivity would develop after switching to another DPP-4 inhibitor in patients with skin rash developed after starting a DPP-4 inhibitor. 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-cell 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 diabetes has 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 polyuric-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 majorization of autonomic balance disorders and the onset of an epileptic seizure (without hypoglycemia), revealed a relapsing-remitting MS, justifying the introduction of an immunomodulatory 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 (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 mg/ml and postprandial at 1.15 mg/ml, glycemia respectively at 1.95 g/l and 2.67 g/l). 4 months after change: fasting C-peptide at 0.51 mg/ml and postprandial at 1.85 mg/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 mg/ml).

Discussion
Although slow-type 1 diabetes or a protective effect of the GLP 1 analogue 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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P479
Treating depression in insulin dependent diabetes improves glucoregulation
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Background
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 absence 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% ± 2.1% to 7.7% ± 0.7% (P<0.001). BDI-II scores improved significantly from 23.5 ± 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 (R²=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 glucoregulation. This therapy did not have any adverse effects on lipid profile or inflammatory status.

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P480
Comparative analysis of multiple daily injection of insulin and continuous subcutaneous insulin infusion regimens 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 progressve 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. Glyceria and glycated hemoglobin were monitored Within 12 months,

Results
The comparative analysis showed a significant decrease in glycated hemoglobin (Z = 0.3) by 2.3% in group 2, compared with children and adolescents on 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 the 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 and delivery at our Institution. Group 2 includes 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. Glyceria and glycated hemoglobin were monitored Within 12 months,

Results
We showed that LGA was significantly higher in women with pre-gestational BMI (7.9 ± 2.8 kg/m2) than in control group 1 (3042.4 ± 282 women were included in each group. There were not significant differences in the incidence of neonates large for gestational age (LGA) and macrosomic values of HbA1c (7.5% reached 50% of patients in groups 1 and 2.

Conclusion
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
Suping Huang, Yongjin Liu & Bwei Huang
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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, anticoagulants, 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), 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 monitoring 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 occurred 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
Rosa Alhambra-Expo´ sito & Marı´ aA´ ngeles Ga´ lvez-Moreno

is added. Variables analyzed baseline and at 6 months after treatment change: age, stabilization in weight loss, liraglutide is suspended and canagliflozin 100 mg

Descriptive study: patients with type 2 diabetes (DM-2) in treatment with progression of weight loss after stabilization with liraglutide 1.8 mg.

To evaluate the efficacy of canagliflozin 100 mg for glycemic control and canagliflozin after liraglutide in patients with type 2 diabetes

P485

Dapagliflozin after liraglutide in patients with type 2 diabetes
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Rosa Alhambra-Expo´ sito & María Angeles Gálvez-Moreno
Hospital Universitario Reina Sofia, Córdoba, Spain.

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 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.

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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Rosa Alhambra-Expo´ sito & María Angeles Gálvez-Moreno
Hospital Universitario Reina Sofia, Córdoba, Spain.

Objective
The change of treatment of liraglutide 1.8 mg to dapagliflozin or canagliflozin 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 or dapagliflozin.

Results
Thirty-three patients (group 1: 18; group 2: 15). Baseline characteristics were similar in both groups. Results at 6 months of treatment change:

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 step in type 2 diabetes, what to choose?**

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Hu Reina Sofia, Córdoba, Spain.

**Introduction**

In type 2 diabetes the choice of the second drug after metformina is marked by the basic characteristics of the patient.

**Objective**

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 TAD were significantly lower on SGLT-2 group. On DPP4-4, only HbA1c levels were significantly lower than basal. On GLP-1, HbA1c and TAD were significantly lower.

<table>
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<tr>
<th>Basal</th>
<th>Final</th>
<th>P-value</th>
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<tr>
<td>Age</td>
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<tr>
<td>IDP4</td>
<td>51.64</td>
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</tr>
<tr>
<td>GLP1</td>
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<tr>
<td>BMI</td>
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<td>Sex (F-M)</td>
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<tr>
<td>IDP4</td>
<td>16-24</td>
<td></td>
</tr>
<tr>
<td>GLP1</td>
<td>14-7</td>
<td></td>
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<tr>
<td>Sex (F-M)</td>
<td>14-7</td>
<td></td>
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<tr>
<td>GLP1</td>
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<tr>
<td>p-value</td>
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<tr>
<td>SGLT2</td>
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<td>IDP4</td>
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<tr>
<td>GLP1</td>
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<tr>
<td>p-value</td>
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<td>Total colesterol</td>
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<tr>
<td>SGLT2</td>
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<td>0.246</td>
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<td>SGLT2</td>
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<td>GLP1</td>
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<td>p-value</td>
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<tr>
<td>p-value</td>
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<tr>
<td>TAD</td>
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<tr>
<td>SGLT2</td>
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</tr>
<tr>
<td>GLP1</td>
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<td>0.007</td>
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</table>

**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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**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 59.2 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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**P488**

**Short term adherence with discharge recommendation for insulin treatment among patients with type 2 diabetes**

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Introduction

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% ± 2.1% in the full adherence group and 7.7% ± 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.

DOI: 10.1530/endoabs.56.P488

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**P490**

**Experience in clinical practice with new long-acting insulins in type 2 diabetes (T2D)**

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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% ± 2.1% in the full adherence group and 7.7% ± 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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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/m². 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 = 0.017) in comparison to 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%; P = 0.037), maintaining BI dose, TDD, U/kg and weight.

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 more pronounced when diabetes age was mainly used in not insulin-treated patients and in those with poor metabolic control. ID was chosen in patients with high insulin requirements, not only to improve glycemic control and weight loss around 5%.

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 pharmacokinetcs 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 homogenous 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/m²): EL: 41.8 ± 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/design

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): –1.5 ± 0.3% vs –1.7 ± 0.3%; P = 0.73; weight loss (SGLT2i vs GLP1ra): –3.3 ± 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 regimen (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), median dose decrease (15.5 [7.5–29.5] vs 14 [8–24] IU; P = 0.90).

Conclusions

Both SGLT2i and GLP1ra as add-on therapy to insulin result in equivalent therapeutical response. More studies are needed to assess the usefulness of these drugs as add-on therapy to insulin in comparison with other antidiabetic drugs.

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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 HbA1c, blood pressure, blood lipids and related factors were analyzed.

Results

After one year management, patients with diabetes compared to baseline HbA1c (%), FPG, 2hPG, HOMA-IR, SBP, DBP, TG, LDL-C, Waist indexes have significant decline (P < 0.05), the control rates of HbA1c, 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 HbA1c, 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 HbA1c to diabetic patients; Age, persons with a lower educational level and high HbA1c 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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Abstract withdrawn.
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 glycolcide, metformin + vildagliptin treatment. The patient had a history of thyrotoxicosis 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 2–3 hours ago, she was 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, HC03:20.3 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: 6.905, HC03:7.3 mmol/l and lactate:18 mmol/l. Bicarbonate therapy was started and hemodialysis has been started. After dialysis her ABG revealed pH: 7.409, HC03:18.7 mmol/l and lactate:7.7 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, HC03:29.5 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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Cognitive status, anxiety and depression in patients with type 2 diabetes mellitus on selective DPP4 inhibitor therapy
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Objective
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=a×ALT/AST ratio) + BMI (+2 if female; +2 if diabetic).

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=0.004–0.06 and P=0.074–0.60, 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 quadruple combination of dapagliflozin, metformin and sulfonylurea with DPP-4 inhibitors (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/m² 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 HbA1c and 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 on the Type 2 diabetes mellitus patients who were prescribed insulin analogs (insulin aspart, lirpo, 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 μU/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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**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 26.9% 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 on 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) was used. 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 (y2 = 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 ± 5.20%) in comparison with the group of patients without the mutant allele (2.72 ± 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 personalization 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, young 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 overweight 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, HCO3: 4.9 mmol/l, pCO2: 19.8 mmHg, at urinalysis ketonuria (3+), glucosuria (1+)]. Intravenous 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: 3.38 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 attended 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 (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 glycemia values during the day.
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P508
Insulin requirements and obstetric outcomes in pregnant women with type 1 diabetes under continuous subcutaneous insulin infusion (CSI)
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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 CSI.
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 CSI was 4.9 years (range: 0.5–12). Statistical analysis with SPSS 22.0.
Results
The average pre-conception HbA1c was 6.90% (s.o.:0.623) and during pregnancy 6.70% (s.o.:0.610). Thougout pregnancy the total insulin requirements increase by 87.5%: from 33.51 (s.o.:8.85) to 62.84 (s.o.:21.16) (Sig:0.00). These modifications compared with the pregestational values are summarized in the following table (Table 1): nine patients experienced miscarriage (23%) none preceded by severe hypoglycemia 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.

<table>
<thead>
<tr>
<th>Time</th>
<th>Total Insulin</th>
<th>Basal Insulin</th>
<th>Carbohydrate-to-insulin ratio</th>
</tr>
</thead>
</table>

All mean, s.o: No sig.
DOI: 10.1530/endobs.56.P508

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 SGLT2) 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 SGLT2.
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 iSGLT2, 2% used dapagliflozin, 6% empagliflozin and 3% canagliflozin. After four months of treatment, there was a significant decrease in weight (100.1 ± 26 kg vs 96.9 ± 25.2 kg), BMI (37.2 ± 8.9 kg/m² vs 35.8 ± 7.6 kg/m²), 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 significant decrease in AST (33.4 ± 26 IU vs 24.9 ± 14 IU), consequently decreasing HSI (hepatic steato index; 47.3 ± 9.4 vs 45.5 ± 9.3). There were no changes in blood pressure, lipid profile or ALT.

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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 + Canagliflozin, 11.3% Liraglutide + Empagliflozin, 16.1% Dulaglutide + Canagliflozin, 8.1% Liraglutide + Dapagliflozin, 6.4% Dulaglutide + Empagliflozin, 6% Exenatide de + Dapagliflozin, 4.8% Exenatide + Empagliflozin, 4.8% Exenatide + Canagliflozin and 1.6% Lixisenatide + Dapagliflozin. At baseline, they had a FPG of 188.4 ± 93.6 mg/dl, an HbA1c of 8.85 ± 1.7%, a SBP of 133.7 ± 12.3 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/m² 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 ± 11.82 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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PS10
Psychopharmacological 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 (CSI) 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 psychopharmacological predictors of CSI satisfaction and QoL improvement in patients on CSI therapy.

Patients and methods
We gather a sample of 49 diabetic patients in CSI 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 CSI usage time of 5.7 ± 2.1 years. We applied the following questionnaires: the CSI satisfaction questionnaire, the perception that CSI is helpful concerning glycemic variability is the most important contributor to QoL (r = 0.43; P = 0.001) and overall QoL (r = -0.43; P = 0.001). The perception that CSI is helpful concerning glycemic variability is the most important contributor to QoL (r = 0.43; P = 0.001). Results point out that patients who check their blood glucose more often tend to report less worries about diabetes complications, glycemic variability and daily self-security (r = -0.35; P = 0.011). 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 = 0.011). Regarding the BSI we noticed that patients with low interpersonal sensitivity tended to report less embarrassment in using CSI therapy (r = 0.45; P = 0.001). We also found that patients with higher obsessive compulsive symptomatology stated more daily activity interference in CSI therapy, namely, wearing desired clothes (r = 0.42; P = 0.003), sleep patterns (r = 0.53; P ≤ 0.001), eating habits (r = 0.30; P = 0.04) and exercising (r = 0.53; P = 0.01). Lastly, family support, reflected in the form of not arguing attitude, seems to be a psychopharmacological protector (r = 0.36; P = 0.01).

Conclusions
In our sample is clear that CSI therapy contributes positively to QoL. However, in order to maximize its impact, it seems relevant to monitor patients’s psychopathological register. Addressing these issues previously will probably provide patients and their families with more adaptive strategies in order to enhance better glycemic control.

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PS11
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 traditionally been 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/m², 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/m²). 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 pregnant women 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.

Results
Mean age of our patients was 32.5±6.4 years, mean pre-pregnancy BMI 27.7±3.9 kg/m². 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 51% 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 (>0.26 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 (Hiijr) 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 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 (Hiijr) 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 FBG 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 for the cause with 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 ± 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 31.9yrs, 32% had gestational diabetes and 68% pre-gestational diabetes. BMI pre-gestational average was 29.27 kg/m² 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?
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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 importance of carbohydrate distribution during the day.

P515
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 patient’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 (DTQ14c) 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 DTQ14c 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 AIC 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 DTQ14c, patients were generally quite satisfied with their treatment with an average overall score to 21/36 ± 2.6. 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 73% 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 patient’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.

P516
Long-term results of continuous subcutaneous insulin infusion on glycemic control and severe hypoglycemics
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Introduction
The use of Continuous Subcutaneous Insulin Infusion (CSI) is expected to improve glycemic control and to reduce hypoglycemic events. However, long-term beneficial results in glucose control are not always observed. We evaluated long-time glucose control and severe hypoglycemics in type 1 diabetic patients using CSI, without continuous glucose monitoring.

Patients and methods
This was a retrospective study of adult type 1 diabetic patients using CSI, assisted at the endocrinology outpatient department of a tertiary hospital. Mean HbA1c was evaluated before CSI and each year thereafter. Severe hypoglycemics were registered in the year before CSI and the last two years of follow-up.

Results
Ninety patients were studied (66% female). They used CSI since 34 ± 10 years and had type 1 diabetes since 18 ± 11 years before. Follow-up with CSI was 6.3 ± 2.6 years. Mean HbA1c at baseline and during follow-up with CSI was as follows: Overall, HbA1c significantly decreased (P<0.001) in the first year with CSI and remained lower than baseline during the first six years of follow-up (P<0.05). However, higher pre-CSI 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>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 hypoglycemics (78% in patients with baseline HbA1c<8%) significantly reduced after CSI (P<0.05).

Discussion
The best glycemic control was observed during the first year using CSI, 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 CSI. In fact, CSI was effective in long-term glycemic improvement in patients with baseline HbA1c≥8%. On the other hand, CSI also reduced severe hypoglycemic events, which affected mostly patients with baseline HbA1c<8%.

Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>HbA1c % (mean±SD)</th>
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<td>Baseline</td>
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<td>All</td>
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<tr>
<td>Baseline</td>
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<td>HbA1c&gt;8%</td>
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P517
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 duration 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 hypoglycemia was 97.05%, 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 (13.7%). 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 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 orexinergic neurotransmitter 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 Department of Internal Medicine.

Material 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 X² 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 and 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 were 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 increases the expression of PPARγ and mTOR on the expression of CPT-1, UCP-2, PPAR-gamma and mTOR.

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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 environmental 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 II 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 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 138 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 0.18–0.90; 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 journalled 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 (CNA). 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.

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Nuclear receptors and Signal transduction

P527

Calbindin-d9k interacts with Mucin1, which influences the stability of Hypoxia inducible factor-1α

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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, HIF1α protein is stabilized and starts transcription. Mucin1 mediates the stabilization of HIF1α in a cytoplasm. In addition, cytoplasmic domain of mucin1 and HIF1α form a transcriptional complex at glycocolic gene promoters. Interestingly, in calbindin-d9k knockout mice, both HIF1α and mucin1 protein 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 HIF1α and mucin1. In the result of western blots, immunofluorescent and immunoprecipitation, calbindin-d9k was identified to interact with mucin1, which influence the stabilization of HIF1α.

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±2% partial pressure of O2. Expression of HIF1α 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 HIF1α 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 HIF1α protein in calbindin-d9k knockout mice might result from the absence of calbindin and mucin interaction.

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Neuroendocrinology

P526

Analysis of the results of fasting test in hypoglycemiass 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 mcu/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/m². 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 FB:AIC 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±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 mcu/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 hypoglycemia.

In view of these data, it could be concluded that it is important to document the Whipple trial before concluding a possible diagnosis of hypoglycemia to avoid unnecessary tests.

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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 23.5, 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; Polymorphisms; 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 time (0.25, 45 and 30 in years). Viscoelastic tissue participants with obesity only and this association is independent of fasting insulin. This study investigated the association of leptin level in high-fat diet-induced obese mice.

Results
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P530
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/m²) undergoing GBS and 62 healthy, age-matched control subjects (mean age 45 ± 10 years; BMI 23.5 ± 1.8 kg/m²). 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=0.256, P=0.048 and r=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.

Obesity

Antioxidant 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 substate-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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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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P532

Using on-line program of good nutrition and weight 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. They 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 ≥ 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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.

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 years 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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P534

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 conjunctive 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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P535

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

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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 trypan 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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**P537**

**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**

Most 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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**P538**

**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 BE2/C2 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 promoter region. Dexamethasone robustly increased AgRP transcriptional

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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±4.4, P<0.00). 

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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P539

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 lose weight, exercise group had no depression while fasting, skipping meals or taking diet pills for their mental health.

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 lose 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 perform overnight polysomnography 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/m²]. The mean age and BMI between male and female patients were not significantly different [55.6±9.0 and 38.3±6.0 kg/m²; 53.8±8.7 and 41.3±8.8 kg/m², 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/m² 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/m² 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/m², 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 reclutated, 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 solution (previous BMI 44.12±6.8 kg/m² vs post-BS BMI 33.4±5.2 kg/m², P<0.001). In the group of BS patients, 83.0% were not previously employed and 3.03% have a job. None of patients that attended 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 WPQ-I-GH questionnaire was administered to all the patients.

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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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/m², 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 (± S.E.M.) age was 43.8 ± 0.13 years; BMI was 23.7 ± 0.02 kg/m²; 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 and promotes muscle metabolism. 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 positively with HDL-C. Consequently, low serum irisin levels might be of clinical 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.
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 food frequency questionnaire. The leptin expression among non-diabetic adults?

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.

Conclusions

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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 ± 10.379, 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, P = 0.018), and CRP cut off points (238.7 pg/ml, 172.8 pg/ml and 0.366 mg/dl) 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 were 0.880, 0.863 and 0.892, respectively. 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 were 0.880, 0.863 and 0.892, respectively. 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 were 0.880, 0.863 and 0.892, respectively. 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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 and acute coronary events in obese subjects, so that oxLDL could be used as 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/m²), 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 analyze the bariatric surgery effects on the comorbidities; and 3) To evaluate the complications of bariatric surgery.

Methods
Cohort study with intra-subject 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/m². Before surgery 26.4% 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 triglycerides were reduced significantly after surgery. 12% of patients had early complications and 17.5% developed later complications (The most frequent complication was eversion). 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/m² 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 1.33 ± 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 in patients with risk factors of diabetes mellitus of type 2 (DM 2) including impaired glucose tolerance/impaired fasting glucose (IGT/IFG).

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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/m²) 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 μM/l 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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P552
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 wheat. 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±6.4 y), 10 overweight (mean body mass index (in kg/m²): 27.5±2.2) and 11 obese (mean body mass index (in kg/m²): 32.7±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

<table>
<thead>
<tr>
<th></th>
<th>White wheat bread</th>
<th>Whole grain bread</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate (g/100 g)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Protein (g/100 g)</td>
<td>8.07</td>
<td>8.61</td>
</tr>
<tr>
<td>Fat (g/100 g)</td>
<td>1.53</td>
<td>1.61</td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>5.61</td>
<td>8.68</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>258</td>
<td>267</td>
</tr>
</tbody>
</table>

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P554
Are there differences in cardiovascular risk between metabolically healthy and sick obese?
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Abstract withdrawn.

P555
The effects of bariatric 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 been 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/m², 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.

DOI: 10.1530/endoabs.56.P555
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.

Objective
To analyze if there are differences in cardiovascular risk between metabolically healthy (MHO) and sick obese (MO), matched by age, sex and body mass index (BMI).

Material and methods
We included patients who underwent bariatric surgery in our hospital. We divided them into two groups (MHO and MO), matched by age (±3 years), BMI (according to the obesity degrees) and 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 MO. The cardiovascular risk measured by Score was significantly lower in the MHO (0.04±0.19), than MO (0.26±0.81). P=0.019. The same happened with the Framingham scale (MOH 0.04±0.190 vs MO 4.04±3.66, P=0.001).

Conclusions
In our series, MHO have a lower cardiovascular risk both for the scale and for Framingham, adjusting for age, sex and degree of obesity.

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P556
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: 68.8±6.0, 62.6±7.9 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/m²), compared to NU (P=0.02). In particular, reduced intravisceral and android fat was noted (CU vs PU, P=0.02 and 0.03 respectively). Total fat mass tended to be lower for CU (P=0.06) with absolute values of 2.2±0.5 and 23±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.


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P557
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 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.

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The objective of the study was to analyze the correlation CIMT and sex steroid levels in severely obese women of reproductive age.

Methods and patients

This was a cross-sectional clinical study. The study included 65 severely obese women aged 35.0±5.2 years, with pre-gestational BMI 35.0±6.5 kg/m². 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 was used as a mean CIMT value.

Results

Anthropometric, hormonal and CIMT data was as follows: TT 124.1±24.9 nmol/l, SHBG 23.1±12.0 mmol/l, androstenedione 2.25±1.2 mg/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 correlation between CIMT and sex steroid levels (P>0.05).

Discussion

We studied preoperatively and postoperatively MPV, NLR, PLR, PLT changes in patients who underwent bariatric surgery. Post op values demonstrated 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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P558

Carotid intima-media complex thickness and sex steroid levels in severely obese women of reproductive age

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Introduction

Obesity is often accompanied by comorbidities predisposing atherosclerosis. Carotid intima-media complex thickness (CIMT) is considered 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 severely obese pre-menopausal women.

Methods

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/m². 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±24.9 mg/dl, BMI 47.8±10.5 kg/m², waist 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±1.9 nmol/l, SHBG 23.1±12.0 mmol/l, androstenedione 2.25±1.2 mg/ml, DHEAS 5.2±3.6 µmol/l, CIMT 0.44±0.1 mm. There was significant correlation between CIMT and weight circumference (P<0.05), without significant correlation between CIMT 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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P559

Effect of pre-gestational weight and gestational weight gain in women with gestational diabetes mellitus on pregnancy outcome

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Objective

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 33.9±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 (1.07–7.38, 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.

DOI: 10.1530/endoabs.56.P559

P560

The effects of endurance exercise training on chemerin, apelin, and visfatin in metabolically healthy obese young males

Sang Bae Lee, Jung Hye Kim, Kahlui Park, Ji Sun Nam, Shinae Kang, Jong Suk Park, Chul Woo Ahn & Yu-Sik Kim

Sang Bae Lee, Jung Hye Kim, Kahui Park, Ji Sun Nam, Shinae Kang, Jong Suk Park, Chul Woo Ahn & Yu-Sik Kim

Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Republic of Korea.

Purpose

This study investigated the exercise-induced changes in novel adipokines (chemerin, 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 healthy 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 compared to C group during 8-wk intervention (-5.96 ± 6.07 vs. 0.75 ± 2.29 ng/mL, Z = -2.64 ± 4.15 vs. 19.0 ± 43.61 ng/mL and -129.4 ± 138.01 vs. 83.08 ± 153.39 pg/mL, respectively, all P < 0.05). The change in serum apelin level was significantly correlated with the changes in fasting plasma insulin (FPI, β = 0.672), homeostasis model for insulin resistance (HOMA-IR, β = 0.603) and β-cell function (HOMA-β, β = 0.696), and quantitative insulin sensitivity check index (QUICKI, β = -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.

DOI: 10.1530/endoabs.56.P560
Obesity is considered as an excessive lifestyle 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 hypodiploid effects of saturated polysaccharide obtained from Codium fragile (CFSIP) 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 associated 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 CRSP administration with no fatty deposits in the liver and a protective effect against renal histological alteration. This confirms the importance of this polysaccharide in the fight against oxidative stress and the prevention of hyperlipidemia.

Keywords: Green alga, Antioxidant, Hyperlipidemia, Liver-kidney functions.

DOI: 10.1530/endoabs.56.P563

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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 dyslipidemia. 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 type 2. 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 in patients over 55 years old.

Results
Serum oxytocin levels in patients with metabolic syndrome were significantly higher (Median = 25 (21–56.5)) than in control group (Median = 19.5 (16–25)) 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 mmol/l versus 34.33 ± 3.38 mmol/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.

DOI: 10.1530/endoabs.56.P565

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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 patients with hypergonadotrophic hypogonadism, who have similar laboratory values of perimenopausal women.

Methods
A total of 230 young male patients with newly diagnosed hypergonadotrophic 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 hypergonadotrophic 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

<table>
<thead>
<tr>
<th>Patients (n = 230)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>21.16 (± 1.79)</td>
</tr>
<tr>
<td>Diag. of KS (n,%)</td>
<td>77 (33.5%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.35 (± 4.03)</td>
</tr>
<tr>
<td>AC (cm)</td>
<td>60.06 (± 35.61)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>71.02 (± 39.51)</td>
</tr>
<tr>
<td>Total-C (mg/dl)</td>
<td>163.46 (± 30.42)</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>347.84 (± 33.66)</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>27.21 (± 14.85)</td>
</tr>
<tr>
<td>T. Testosterone (ng/dl)</td>
<td>0.93 (± 0.93)</td>
</tr>
<tr>
<td>F. Testosterone (μU/ml)</td>
<td>8.31 (± 13.56)</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>22.48 (± 18.67)</td>
</tr>
</tbody>
</table>

DOI: 10.1530/endoabs.56.P567

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 ± 8.85 years. The BMI before the intervention was 47.29 ± 5.54 kg/m² being 34.52 ± 6.48 kg/m² 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/m², and as normal weight if BMI between 18.5 – 24.9 kg/m². 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 78.2 ± 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 = 0.291; 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 for dyslipidemia.

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P570
Abstract withdrawn.

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Effect of 8 weeks of hypocaloric diet and physical activity on thyroid hormones, insulin 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 lifestyle intervention on insulin sensitivity, insulin concentration and thyroid function parameters.

Methods
A randomized interventional clinical study (NCT02325804) included lifestyle 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, insulin 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 (ISI M and ISI C ed).

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 ≤ 0.000 1), insulin sensitivity improved (IR HOMA 2.71 ± 3.90 vs. 1.24 ± 0.83; P = 0.01; ISI M 6.64 ± 4.38 vs. 8.93 ± 5.36; P ≤ 0.000 1; ISI C ed 59.1 ± 21.4 vs. 64.7 ± 22.5; 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 insulin significantly decreased after intervention (233 ± 66 vs. 167 ± 88 mg/dl; P ≤ 0.000 1) and positively correlated with ISI M at, however only after intervention (P = 0.05).

Conclusion
Results of our study are in line of previous results suggesting beneficial effect of intensified lifestyle changes on insulin sensitivity and thyroid function. Novel view indicates that changes in thyroid-stimulating hormone (TSH) could well be a light greater decrease in weight that GG homozygotes (A carriers: P = 0.047; GG homozygotes: P = 0.000 1). We observed a continous weight gain in our kidney transplant patients. When different obesity criteria 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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The comparison of different obesity criterias in kidney transplant recipients
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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 cohorts 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 study 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/m2; 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 e-LDL according to the baseline (total cholesterol: −15.47 ± 21.01 mg/dl, P = 0.008; e-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.

DOI: 10.1530/endoabs.56.P573
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.

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, 40 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 was 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.

DOI: 10.1530/endoabs.56.P576
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/m², 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/m² and to 35.11 ± 7.28 kg/m² 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 ± 66.64 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 ± 1.28 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 LSG determines both short and long term improvements in weight loss and metabolic parameters.

DOI: 10.1530/endoabs.56.P579

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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/m²) 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 5.44 (±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.

DOI: 10.1530/endoabs.56.P578

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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**

C57Bl/6 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.

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that involves downregulation of mTOR/p70 S6K signaling pathway.

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.

Conclusions

Results suggest that in heart of obese rats, IGF1 mitigates detrimental effects of obesity by increasing expression of SOD 1 protein, probably through mechanism involving downregulation of mTOR/p70 S6K signaling pathway.

PS581

Plasma metabolic 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 animals, is closely associated with type 2 diabetes mellitus, obesity and cardiovascular diseases. 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 animal 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 a BMI of 27.6 ± 3.9 kg/m². At the moment of conception the maternal mean age was 33 ± 4.6 years and the BMI was 30.6 ± 4.9 kg/m². 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). Gestational 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 increase the risk of prematurity or complications during pregnancy. We found an increased risk of small-for-gestational-age compared with general population.

PS582

“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 premature 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/m². At the moment of conception the maternal mean age was 33 ± 4.6 years and the BMI was 30.6 ± 4.9 kg/m². 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). Gestational 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.

Conclusion

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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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 (MTP) 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, PEP1T 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 MTP, NHE3, SGLT1, GLUT2, GLUT5, PEP1T, FATP4, CD36/SR-B2 and NPC1L1. PKA and PKC activities were analyzed by ELISA.

Results
HFD consumption from third up to 12th week increased MTP and NHE3 content, but decreased the GLUT2, PEP1T and NPC1L1. HFD also increased 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 PYY and PKA activities by 12th week.

Conclusion
Considering that mice began to gain weight from the third week after HFD consumption, the reduction of GLUT2, PEP1T 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 MTP and NHE3, we could infer that MTP 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 PYY and PCK activities, at least for the NHE3, whose activity is known to be decreased by PCK.

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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 ± 3.9 kg/m², 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 ± 4.6 vs. 4.6 vs. 0.48 ± 3.9 vs. 1, 2 ± 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 what 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 regulation and 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, overweight, 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 cells-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 sulphhydril (SH) and malondialdehyde (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/m², 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) x fasting 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 vs 1.9±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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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 hypoeogenic 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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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 (C3), 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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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, rs10487500, 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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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 life was assessed, 6 months after sleeve gastrectomy by the baroqs of 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 43.5%. 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 referred 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/m². 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 (53%) had a folic acid deficiency. Average folic acid intake was 394.53±168.34 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 significant statistical association.

Conclusion
Our data suggest that Obesity is a risk factor for folic acid deficiency. This deficiency is likely to worsen after bariatric surgery. Therefore, a preoperative nutritional assessment is important to detect and correct Folic acid deficiency.

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Activation of p53 with low doses doxorubicin reduce the accumulation 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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Association of dietary factors and dynamic thiol/disulfide homeostasis in subjects with coronary artery disease

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**Background**

Environmental factors such as lifestyle changes and dietary 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 early indicator for CAD. There is limited data on the relation of dietary factors with thiol/disulfide homeostasis in patients with CAD. Therefore, 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 automated 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) carbohydrate 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-carotene were similar in CAD and control group except thiamine (P=0.047). There was significantly lower intake of minerals in CAD. Carbohydrate 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 disulfide 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. Carbohydrate 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/m²) 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/m², P<0.001), 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% CI 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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**P595**

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 ≥ 40 kg/m²) 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 (BodPod) 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/m²) occurred 24 m after RYGB in group A (28.3 ± 0.6 kg/m²), and 18 m after surgery in groups B (28.3 ± 0.7 kg/m²) and C (30.8 ± 0.7 kg/m²). The mean nadir of percent body fat was greater than 30% in all three groups (A: 33.8 ± 1.2%; B: 35.2 ± 1.4%; C: 36.5 ± 1.3%). The percentage reduction of BMI respect to baseline was lower in group C compared to group A at 24 m (30.1 ± 3.5% vs. 34.4 ± 1.3%; P<0.01), 36 m (28.1 ± 4.8% vs. 33.2 ± 1.6%; P<0.01) and 48 m post RYGB (25.7 ± 3.9% vs. 31.7 ± 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 ± 1.7% vs. 35 ± 1.7%; P<0.05) and 36 m (27.4 ± 2.9% vs. 36.2 ± 2.2%; P<0.01), 24 m (21.9 ± 1.6 vs. 33.9 ± 2.5%; P<0.01) and 48 m (13.8 ± 2.3 vs. 30.3 ± 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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P596
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 dietary 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/m². 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.

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-microbiota interactions for the beneficial effects of surgery. This study aimed to assess whether the altered gut microbiota 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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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 analyses 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, linear 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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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 1:20 minutes. CIT was defined as the difference between EE during cold (EEcold) and warm (EEwarm) 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 (EEwarm) and cold (EEcold) conditions and the movement speed of the pressure center increased from 113.6 ± 9.9 mm/sec to 114.0 ± 2.2 mm/sec, P = 0.01 (95% CI: 3.04; 15.81), speed index changed from 113.0 ± 9.1 to 114.0 ± 2.1, P = 0.01 (95% CI: 3.0; 16.1) and overall rating movement reduced from 109.9 ± 6.8 to 109.0 ± 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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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/m² (average BMI 40.9 ± 9.3 kg/m²). 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 stabimetry (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/sec, P = 0.005 (95% CI: 2.86, 12.14). According to the stabimetry data the coefficient of stability improved from 113.5 ± 9.1% 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 114.0 ± 2.2 mm/sec, P = 0.01 (95% CI: 3.04; 15.81), speed index changed from 113.0 ± 9.1 to 114.0 ± 2.1, P = 0.01 (95% CI: 3.0; 16.1) and overall rating movement reduced from 109.9 ± 6.8 to 109.0 ± 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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P603
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 aAMP 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 arms 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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P604
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-DXA 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: 89.8 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: 1.365 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.
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 5.81 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% 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.

Paediatric Endocrinology

P608
rs1800497 polymorphism of the DRD2 Gene association with plasma leptin and dopamine Levels in obese and lean children

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Background and aim
The Taq(r)rs1800497 polymorphism of the Dopamine Receptor type 2 (DRD2) gene allele has been commonly related to increased ad lip food intake, weight gain, and risk for obesity overeating and risk for obesity. We supposed to find associations between body mass index (BMI), the Taq(r)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) (≥2 s.d.s., n=98), the 3rd – extreme obesity (EO) (≥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); the 2nd – decreased D (4.99 – 11.64 pg/ml); the 3rd – increased D (11.65 – 60.00 pg/ml); the 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 L (23.79 – 40.18 ng/ml); the 4th – high L (>40.18 ng/ml).

Statistical analysis were performed by means of SPSS 21.0 (χ2-criterion, likelihood 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 Al Taq(r)rs1800497 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 Taq(r)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 type 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 (TIDM).

Patients and methods
98 adolescents (42 boys, 56 girls) 12–16 y.o. with TIDM were examined. The duration of the disease was: less than 1 year in 25 patients (HbA1c 7.4 ± 0.3%) - group 1, from 1 to 5 years in 40 patients (HbA1c 8.9 ± 1.2%) – group 2, more then 5 years in 33 patients (HbA1c 10.3 ± 1.7%) – group 3. Control group: 40 healthy adolescents 12–16 y.o. The indexes of thrombocyte aggregation (degree, speed and time of aggregation) measured by laser method with different inducers (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 comparison of control group (P < 0.05). Levels of ADP and kollagen-stimulating 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 comparison of control group.

Conclusions
Functional activity of thrombocytes in adolescents with TIDM appeared to increase in correlation with duration of the disease and it may demand treatment with heparinoids.

DOI: 10.1530/endoabs.56.P610

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 ± 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 pmol/l, pCort < 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 19 ± 0.3, Veh-female 375 ± 351, Cort-female 3.9 ± 1.4, pCort < 0.001, pCort × Sex = 0.015). 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.

DOI: 10.1530/endoabs.56.P611

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 hypoglycemia 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 insulin aspart). She applied to emergency clinic with diabetic case with recurrent ketosis after U-300 glargine. 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.

We started her routine basal- bolus insulin treatment with U-300 glargine insulin glargine and insulin aspart. We observed again ketones (+2 positive) in urine analysis 10 hours later under her routine basal bolus treatment.

Conclusions
U-300 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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Endocrine Abstracts (2018) Vol 56
Poster Presentations: Environment, Society and Governance
Diabetes Therapy

**P613**

**Safety and efficacy of the available oral anti diabetic drugs in treating type-2 diabetes during Ramadan1437**

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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 diabetes 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 aforementioned were enrolled into the study.

Results

This study concluded that mean total HbA1c improved during Ramadan (P<0.0001). 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 hypoglycemia 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 anti diabetic 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), 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 Mlk3 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, Ry2, Calm2 and Mlk3 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.

**DOI:** 10.1530/endoabs.56.P614

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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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 C57b16 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.

**DOI:** 10.1530/endoabs.56.P615
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 31st 2016 using administrative health databases of hospital discharge forms, certification of chronic diseases, drug prescriptions, specialist outpatient, 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 where national registries on acromegaly are not available.

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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

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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 better learn about their experience and how this could be improved. Two separate acromegaly patient panels and personalized approach.

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 2–10yrs.) 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.
Overuse of laboratory and ultrasonographic examinations in thyreoidology: Study from the Slovak Republic

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Objectives

Slovakia is gradually implementing health technology assessment (HTA). This method evaluates the issue of possible overuse of laboratory and imaging investigations in thyreoidology 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


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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Restless legs syndrome in population of patients with thyroid disease in comparison to general population – 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 that 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 (Δ = 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.

DOI: 10.1530/endoabs.56.P620
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 hoorcappum 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. Summariy, 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 ± 13.1) treated with prednisolone and 30 dialysis patients (19 males, mean age 59 ± 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=27) passed locally applied glucocorticoids for as long as possible. Normal adrenal function was defined as P-cortisol ≥ 420 nmol/l 30 min after Synacthen injection, as validated for the local Roche Elecsys® Cortisol II assay.

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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 rate (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 χ²-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, MetS did 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 (HFpEF), 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...
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 tricuspid 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**

Multihormonal 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 ± 9.12 mmHg vs 112.2 mmHg ± 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 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 ≥ 18 yrs (mean age 30.98 ± 9.1 yrs) underwent MRI angiography using Gadofolinium 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/m² (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/m², 32.14% (n = 18) had aortic dilatation confirmed after calculating the AD/DD ratio (≥ 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/m² vs. 22.8 mm/m², P < 0.001; D2 14 mm/m² vs 17.6, P < 0.001; D3 15.26 mm/m² vs 19.49 mm/m²). The size of the aorta correlated with age in all positions (D1 r = 0.362, P = 0.006; D2 r = 0.356, 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. Multivariable 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 ProtecCAP trial and 359 from the STEP trial. Serum FGF-21 on admission was significantly correlated to disease severity as measured by pneumonia severity index (R² = 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, 0.39–0.81; 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. Hyponatraemia is a known adverse effect of most SSRIs including duloxetine and can potentially be life-threatening. Duloxetine induced hyponatraemia, however, is relatively rare specially on low doses and is typically seen in the elderly frail patients. We report a case of duloxetine-induced hyponatraemia 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 Fludrocortisone 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, disorientation and recurrent vomiting. Laboratory findings revealed hyponatraemia, low serum and raised urine osmolalities, and increased urine sodium. Her TSH and Cortisol levels were normal. Syndrome of inappropriate antidiuretic hormone was consisented and, duloxetine was discontinued. She was treated with fluid restriction, and required intravenous sodium chloride administration 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 hyponatraemia, 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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**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 neuro-degenerative 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 was diagnosed with short stature due to GH deficiency, after that, based on decreased calcium and PTH levels, hypoparathyroidism was recognized and supplementation 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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**Introduction**

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 underwent total thyroidectomy for multinodular goiter. Pathology report revealed a macrofollicular variant of follicular thyroid
A rare mediastinal signet-ring cell carcinoma revealed after postpartum thyroiditis – a coincidence or a link?

Cristina Ene1, Ramona Bica2, Magdalena Zidu2, Aida Mihailovic1, Adrian Istrate1, Ana-Maria Tanase1

Introduction
Postpartum thyroiditis is an autoimmune process that occurs in 5% of the women, precipitated by immunological rebound. The majority of 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 complaints 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 mediastinal 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 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 is it 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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Introduction
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 (identihpned 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 bechtre’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<sup>nd</sup> 4<sup>th</sup> 9<sup>th</sup> 15<sup>th</sup> weeks): TSH - 0,024/ <0,01, 32,139/ 4,69 μU/ 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/ 9/ 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 μU/ 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 department.
consultation 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 evolution pattern, even in the context of significant analytical hypothyroidism. Within our knowledge, the association between Subacute Thyroiditis, Behçet’s Disease and Psoriasis has never been reported. In the future, 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 osteopenia. 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 osteopenia. She was referred to another hospital with haemoglobinopathy service for joint fertility management. A 50 year old lady with transfusion dependent beta thalassaemia major had diabetes mellitus, osteoporosis and premature ovarian failure. She is currently on norvasp, 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 haemodilution. 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 osteopenia 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 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 treatment and ensuring adequate quality of life in these patients.

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].

References

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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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**Objectives**

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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**P641**

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 ultrasoundography (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, pKTV, 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, pKTV 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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**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-hydroxynonenal (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 perox 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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**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
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 thyroidecmy 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 with 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 patients 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 mg/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, Goser, Autoimmunity, Leptin.)

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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 January/2016 to September/2017. 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 autoimmune in selected patients was negative (anti-GAD antibodies for diabetes, and anti-thyroid peroxidase, anti-tireoglobulin, anti-TSH receptors in 2 thyrotoxicosis).

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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 consistent 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 12.2 mg/dl; PTH 113 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 affected 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€œexpanded prostate cancer index composites 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 than patients having surgical 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 may be also useful indicators to judge a response to the treatment. Presently, we do not have 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 class 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. Throid hormones T3 and T4 act as non-classical proangiogenic modulators mediated by non-genomic mechanisms via cell surface receptor integrin αvβ3. 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 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 class 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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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 (ERα) 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 intrinsic 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 cell migration and epithelial–mesenchymal transition.

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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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 type 2D 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 (10μM), 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 GBM 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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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 Identify fibroblasts- expressed kinases that modulate tumor invasion and Chemokine expression, which those 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). 24 h after transfection, fibroblasts were co-cultured with MDA-MB-231 for 3Dpheromons formation. Matrigel and chemotactractants were added to promote invasion that was evaluated by spheroids pictures analysis, kinases silenced spheroids were compared to controls. We identified PKCδ, whose silencing decreased TNBC invasion rate, suggesting a pro-invasive role of this kinase. PKCδ is essential for regulating chemokine production in leukocytes and promotes migration during inflammation. It has been shown that PKCδ inhibitors (CAL -101) interfere in tumour-stroma interactions without directly killing cancer cells. Despite PKCδ being expressed mainly in leucocytes, we detected high PKCδ protein expression in various fibroblast cell lines and in primary fibroblasts derived from TNBC patients; however, PKCδ 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 effects on breast cancer cells. Fibroblasts treated with CAL -101 showed a decreased AKT phosphorylation, a downstream target of PKCδ. Pretreatment of fibroblasts with CAL -101 significantly decreased TNBC cells’ invasion in both 2D and 3D coculture experiments. Interestingly, using transwell systems we found that co-culture of TNBC cells and stromal fibroblasts induced a pro-invasive mechanism 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 PKCδ fibroblasts expression. Using a novel 3D co-culture invasion assay, we identified stromal PKCδ as a key mediator of TNBC invasion. Our results suggest that targeting PKCδ in the tumor microenvironment may represent a novel strategy for TNBC therapy.

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P655
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 (RPWE-1 cell-line and primary cell-cultures obtained from prostatoplastectomies) by analysing different functional parameters such as cell proliferation, cell migration, tumourospheres 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 (RPWE-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-0.1 nM), being this inhibitory effect significantly greater in PCa cell-lines compared to normal prostate cells (RPWE-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 tumourospheres colonies formation in all PCa cell lines tested. Moreover, treatment with Pladienolide-B dramatically reduced the expression of proliferation markers (Ki67 and PTG), EMT markers (Vimentin) and markers of PCa aggressiveness (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, ESRRP1 and ESRRP2. 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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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 the 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 anti-human 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, ×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 fully 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 (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 anti-human 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, ×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 therapeutical 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

Dream recall and content vs the menstrual cycle: a cross-sectional study

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Introduction
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. Prepubertal girls 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 and methods
We studied 779 women (mean age ± s.d.: 31 ± 9 years). The subjects were given a simple questionnaire with items regarding age, menstrual cycle duration, day of menstrual cycle, dream recall regarding previous night’s dreams and dream affect/emotional content (positive or negative). We studied only women with self-reported 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). Conclusion
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; 4.3%) 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-thyroidperoxidase 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 2.5%; P = ns). On the contrary, among euthyroid women, RPL rate was higher in those with PD than in those 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 audiometry, 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 years (30.2 ± 9.9 years) and 65 age-matched healthy women (age 29 ± 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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P661 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 LFTs (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
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 younger age. Bicuspid aortic valve (BAV) and aortic dilatation, both associated with TS, are risk factors. Preliminary studies suggested that cardiac MR (CMR) performs better than transthoracic echocardiography (TTE) for evaluating BAV and aortic dilatation, probably related to the frequent chest abnormalities in TS.

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 assessment using CMR was not possible in 20.5% (46/78) 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 who 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 multidisciplinary approach.

P663
Growth hormone IGF axis - basic

IGF-I correlates with cognitive status in eord patients undergoing haemodialysis
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Background
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-I, IGFBP 3, erythrocytes and hemoglobin (P<0.001, P=0.004, P<0.001, P=0.002 respectively).

IGF-I 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-I 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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P664
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 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 participated in this study and were randomly divided into two groups of 11 individuals. Anthropometric and clinical data of the athletes were: age (18.5±1.1 years), body mass index (22.5±2.1 kg/m²), fat percentage (16.5±3.5%), lean mass (50.1±4.2%) and muscle mass (20.1±2.6%). All the athletes underwent resistance training twice 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-I, IGFBP 3, erythrocytes and hemoglobin (P<0.001, P=0.004, P<0.001, P=0.002 respectively).

IGF-I 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-I 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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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 this 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 hydroxchloroquine 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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P667
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), Z = 0.777). TM showed a small increase in total STAXI-2 scores after three months, compared to baseline (+ 0.90, 95% CI 0.37–1.75, Z = 0.041), decreasing after one year (− 1.296, 95% CI − 2.15 to − 0.44) to scores comparable to baseline (Z = 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 (FANAS) experienced more anger proneness (p = 0.113, Z = 0.003). Over 36 months in TM (prospectively), anger proneness was positively correlated to negative affect (p = 0.415, Z < 0.001) and SCL-factors somatization (p = 0.075, Z = 0.033), paranoid ideation/psychosis (p = 0.101, Z = 0.004), depression (p = 0.082, Z = 0.019) and interpersonal sensitivity (p = 0.119, Z = 0.001). In TW, STAXI-2 scores did not change over time (Z = 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. DOI: 10.1530/endoabs.56.P667

P668
Cigarette smoking and neuroreceptors genetic variations: a handshake between genetic and environmental factors leading to nicotine addiction
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Cigarette smoking 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 CHRNA4 is cholinergic receptor beta polypeptide. Studies have revealed a strong association between nicotine addiction and genetic variants in NRXN1 and CHRNA4 genes in different world populations. Genetic associations of rs6721498 and rs17487223 SNPs of NRXN1 and CHRNA4 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 CHRNA4 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. DOI: 10.1530/endoabs.56.P668

P669
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 OPRD1 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 OPRD1 receptor in drug addiction and cortisol as a stress response, present study was designed to investigate association of the risk allele of rs569356 OPRD1 variant with stress response in Pakistani opioid addicts. Whole blood samples from opioid addicts were collected for the extraction of genomic 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 χ²-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). DOI: 10.1530/endoabs.56.P669
P670
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 allele. 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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P671

Abstract withdrawn.

P672

Abstract withdrawn.

P673
Nuclear Receptors and Signal Transduction
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)2vitamin D3 (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-10-7 M and 10-10 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, Nxia, Bcl-2, Bax, p21, Notch-1 and Notch-2 genes implicated in apoptosis and cell cycle arrest, was evaluated by qPCR.

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 (10-7 M) and then co-incubated with Dex (10-10 M) as compared to cells incubated with Dex (10-7 M). VitD exerts inhibitory effect against Dex induced-apoptosis in Kasumi-1 cells via regulation of Notch signaling but its effect was dependent on the concentration.

Conclusions
VitD exerts inhibitory effect against Dex induced-apoptosis in Kasumi-1 cells via regulation of Notch signaling but its effect was dependent on the concentration. 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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P674
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. 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 $10^{-11}$ M to $10^{-6}$ M) alone or in combination with VitD ($10^{-8}$ M). Epithelial–mesenchymal transition (EMT) markers were evaluated by IF in parental and EVER cells, even after VitD treatment. mRNA PCR Arrays were employed to investigate the difference in parental and EVER cells after 12h of treatment with VitD. EVE-long term exposure increased mRNA and protein VDR expression in PLC/PRF/5 EVE 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 efficiency at concentration ranging from $10^{-3}$ M to $10^{-6}$ M. In EVER cells, EVE $10^{-3}$ M chronic treatment increased the protein expression of mesenchymal markers, but VitD prolonged treatment restored epithelial markers protein expression. mRNA 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 metallokinase 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 reversion EMT and downregulating the expression of genes involved in drug resistance acting through the regulation of miR-375.

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**P675**

**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 also function as a scaffold protein, demonstrating its novel role in protein-proteins. Using improved FlAsH-based lysines in the interaction can be triggered at physiological levels of PKC activation. We found that heterologous mechanisms of interaction are activated at physiological levels of PKC activation. We found that heterologous mechanisms of interaction are activated at PKC stimulation and receptor cross-talk. In this study, we demonstrated that activation of protein kinase C (PKC) by phosphor myristate acid, Gp11-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 paracrine 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 BREIT (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_16-1-2016-0030).

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**Obesity**

**P676**

**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 diagnostis 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**

**P677**

**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 adenocortical tumours (ACT) and participation was 39%.

P678 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/m². Median follow-up duration was 15 (6–21) years. At last assessment 5 (45.5%) had hypothyroidism, and were on thyroxine replacement.

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 persist 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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P679
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 Greulich 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 ± SD) of 7.61 ± 2.23 years. The most frequent clinical presentation was precocious puberty (66.7%) followed by virilization (22.2%) and precocious puberty + acne/rostte 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%), P453S in heterozygosis (5.6%), V281L/P453S (5.6%), P453S in heterozygosis (5.6%) and Cluster E6/V281L/L307 frame-shift/Q318X (5.6%). Of the 36 alleles studied, the V281L mutation was found in 75%. Mean bone age advance was 1.83 ± 0.71 years.
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-Dihydyrotestosterone (DHT), 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 pharmacologically 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 1.74% and 3.02% 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, which is essentially the same orientation as Dihydrotestosterone (DHT) and like testosterone. 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 dependent 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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P682
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 immunosassays, including enzyme-linked immunosorbsent 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 ~ 1.75 nM) for corticosterone as CBG in the sample prior to immuno-absorption (Kd ~ 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. DOI: 10.1530/endoabs.56.P682

### 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 23.4 ± 5.6 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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**P684**

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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**P685**

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 pheochromocytoma. The patient remained normotensive until the age of 29. Only then, after repeated MIBG, laparoscopic bilateral adrenalectomy was performed and two solid heterogenic lesions measuring 16 and 30 mm, on the right and left adrenal glands, respectively, were removed. Histological analysis confirmed 4 benign pheochromocytoma. 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)

P686

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 amenorrhea. There was no easy bruising, or striae.

Diagnosis and Treatment
On presentation BMI was 50 kg/m2 with 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 range 17-OHP and serum testosterone was normal. 24-hour urinary free cortisol excretion was high at 280 (normal range 17.0–200 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 pg/l; normal range 0.1 to 47). Pituitary MRI demonstrated a 12×10 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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P687

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.

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±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 ≥2 or normalized ACTH/prolactin CS(IPS)/P basal ratio ≥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 (transphenoidal 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 ≥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 ≥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 phaeochromocytoma 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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P688

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 morbidity 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.

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/m2; 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 10.6) 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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Clinical case reports – Pituitary/Adrenal

P689
Absent adrenarche in adults with congenital hypopituitarism

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Abstract withdrawn.

P690
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 puberty 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/m2. 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 nM/l, follicle stimulating 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 hypophysis. 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, FSH 1-2. No dysmorphic features. We repeated blood test: TT 0.20 ng/ml, sex hormone binding protein (SHBG) 89.8 nM/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 hypophysis. 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 39.1 nmol/l. Spermiogram persisted in cryptospornozoospermia hypospermia. According to TT levels we suspended HCG treatment and schedule a blood test to treat?

P691
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 hypokalemia (126 mEq/L) and hyperkalemia (5.7 mEq/L) with low glucose levels. Fluid therapy with a dextrose solution was necessary to maintain normal glucose levels. 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+</td>
<td>136-146 mEq/L</td>
</tr>
<tr>
<td>K+</td>
<td>3.5-5.1 mEq/L</td>
</tr>
<tr>
<td>Cortisol</td>
<td>&gt;18 mg/dl</td>
</tr>
<tr>
<td>ACTH</td>
<td>4-20 pg/ml</td>
</tr>
</tbody>
</table>

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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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 therapy. 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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**P693**

**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 1.1 mkg/dl (6.2–10.2) 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 syncpe, 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 μg/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 re-evaluation the hypothyroid-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 (0.1-10.2), TSH 15.5 μIU/l (0.4-4.0), free T4 18.6 pmol/l (11.5-22.5), insulin 11.6 mIU/l (5.0-25.0), C-peptide 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 mmol/l (3-12), GH 0.4 μIU/l (0.16-13.0), IGF1 238 ng/ml (117-329), prolactin 548.6 mIU/ml (40-390). After insulin-induced hypoglycemia there was an absence of cortisol and ACTH increase – cortisol remained 19.4 mkg/dl, ACTH <0.1 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 syncpe were excluded. Patient discharged on hydrocortisone 25 mg and levothyroxine 100 mg 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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**P694**

**Clinical case of exogenous Cushing Syndrome during injections and on topical glucocorticoids**

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Background

Topical glucocorticoids (GCS) are seen 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).

Case reports

**P695**

**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 transsphenoidal 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, levotyroxine, hydrocortisone, estrogen and progesterone. After 5-years of follow up period, some clinical features such as; enlargement of hands and feet, macroglossia and malocclusion 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 performed 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. Transsphenoidal 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 gammaknife 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

Gu¨lay Simsek Bagir & Melek Eda Ertorer
Filiz Eksi Haydardedeoglu, Okan Bakiner, Emre Bozkirli, Pasireotide a new option for acromegaly

Dragan Tesic1, Predrag Petrovic2, Tatjana Pesic2, Edita Stokic1, Milocea Medic1, Milena Mitrovic1, Dragana Tomic/Naglic1, Tijana Icin1, Ivana Bajkin1 & Mirjana Tomic1

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Introduction
Acute hepatic porphyria is a relatively rare metabolic disorder. Its typical clinical manifestations 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 appendixitis. 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 of the 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% glucose and 1000 ml Ringer solution was administered. Tomorrow 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 collapse and respiratory arrest. Na at that moment was 113 mmol/l. Patient was successfully reanimated. That day received 10 g 24 h of sodium chloride and only 3 g 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% SalNaCl) 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. The next morning Na was with only one dose of 3 g NaCl. We confirmed acute hepatic porphyria by porphobilinogen of 67, uroporphyrin 455 and coproporphyrin 1333 mmol/l in urine. During the treatment potassiam 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 hyponatraemia, whatever its cause is. Sodium increase 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 afraid of cardiac arrythmias in case od low potassium, we should escape raised intracranial pressure symptoms of low sodium. Patients xyster, also with porphyria, died suddenly when she was 20 y. old.

Conclusions
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.

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 (18x18x19 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 leptomenigeal 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 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 g 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, even a slight decrease was observed. IGF1 levels were still high. Despite these regimens, the biochemical markers were still elevated, visual field defects were still 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 and 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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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.

**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-year-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 transphenoidal 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 mix 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**

Hyppogonadism 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 partial (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. 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 neurosarcomatoidosis (NS) can be challenging. We describe an unusual 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 infunduloneurohypophysis. In the following years, he developed a panhypopituitarism, which was correctly substituted. 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 pleocytosis and elevated protein level, whereas beta-HCG and alpha-fetoprotein were negative. A chest CT only showed few mediastinal adenopathies. An elevated serum angiotension converting enzyme level was documented, whereas antimuclear 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.
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 with 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 stT4: 0.74 ng/dl (normal range: 0.89–1.37), stT3: 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 stT3: 2.95 ng/dl, stT4: 0.95 ng/dl and TSH: 1.13 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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P702

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 woman 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 (IPS) was ordered but it was cancelled because clinical and biochemical hypercortisolism disappeared. Three months later, hypercortisolism appeared and immediately IPS was made. IPS was diagnosis of a central source for ACTH secretion. The patient was treated successfully with transphenoidal hypophysectomy. Histopathology revealed a 4.5 mm pituitary corticotroph microadenoma. After that, they were normalized 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 asymptomatic. IPS should be made only when biochemical hypercortisolism is present at the same time.

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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, dia phragm 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 September of 2016 at 103.4 nmol/l. Patient underwent 5 week radiotherapy early 2017. Lanreotide was then increased to 90 mg SC due to slight increase of IGF-1 levels from 94 to 35 nmol/l; currently on an increased dose of Pegvisomant from 10 to 15 mg SC due to lack of response this was increased to 90 mg. Medication was eventually stopped after 3 months due to nausea, abdominal discomfort, dia phragm 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 September of 2016 at 103.4 nmol/l. Patient underwent 5 week radiotherapy early 2017. Lanreotide was then increased to 90 mg SC due to slight increase of IGF-1 levels from 94 to 35 nmol/l.

Conclusion

Management of acromegaly is complex and requires extensive input from both surgical and medical specialties. Debuking 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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Background
Acute invasive fungal sinusitis (AIFR) is a rare but fatal infection that occurs primarily in immunocompromized individuals. It is characterized by fungal invasion into the mucous and submucosal structures of the paranasal sinuses with extension into adjacent structures, including the parasanal 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 hypopitatemia due to unknown origin and transferred to our hospital for further examinations. He presented body weight los, right eyelid ptosis and oculomotor movement disorder. Laboratory data showed severe hypopitatemia (Na 119 mEq/ml) and hypopituitarism (ACTH 8.8 pg/ml, Cortisol 4.3 µg/dl, TSH 1.1 µIU/ml, T4 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 sinus, which considered as culprit lesion of right eye symptoms. A stenosis of right internal carotid artery due to AIFR. Antifungal agents (VRCZ, MCFG) and hormone replacement therapy (hydrocortisone, LTI) were started, and tumor general fatigue, hypopitatemia, 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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P706
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. Laboratory tests indicated hyperglycemia, metabolic alkalosis, thrombocytopenia (15,000 elt/mm3) 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 53x27x25 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 havent 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 hypercortisolemia 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 of 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 adamantinomatous cranopharyngioma 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

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Performed at experienced centers and TSS should be considered as priority. Diagnosis and follow-up during pregnancy. Management of patients should be performed at some point to exclude lesions in the hypothalamo-pituitary axis and may not resolve in 2 years 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. The basal biochemistry, the serum Na level was 143 mmol/l, serum osmolarity was 293 mosm/l. The urine osmolarity was 93 mosm/l. She was hospitalized for water deprivation test. During the test, urine osmolarity did not change with water deprivation but became 5200 concentrated after vasopressin which was compatible with central DI. In the pituitary MRI neurohypophyseal T1-bright spot situated ectopically in the infundibulum. Desmopressin nasal spray 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 done in the post partum period. After delivery pituitary MRI should be performed at some point to exclude lesions in the hypothalamo-pituitary region.

P710 A case of diabetes insipidus 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 present 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 clinic 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. The basal biochemistry, the serum Na level was 143 mmol/l, serum osmolarity was 293 mosm/l. The urine osmolarity was 93 mosm/l. She was hospitalized for water deprivation test. During the test, urine osmolarity did not change with water deprivation but became 5200 concentrated after vasopressin which was compatible with central DI. In the pituitary MRI neurohypophyseal T1-bright spot situated ectopically in the infundibulum. Desmopressin nasal spray was started and the symptoms resolved immediately.
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Progressive optic glioma and concomitant precocious pubert y: 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 endocrinopathies. Signs of such involvement can include growth acceleration 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 carcinologist. 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 (± 3SD). Breast development were compatible with Tanner stage 3 and no pubic hair was present. Ultrasound imaging showed ovoids were prominent (right ovoid: 2 × 1 cm and left ovoid: 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 mIU/mL, LH level of 2.63 mIU/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 (tropoelin acetate 11.5 mg every 3 months). During follow up, 6 months of starting treatment, his progression of puberty has been arrested. With the 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 anhidrosis/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. This rare condition revealed partial endodontics with a single tooth erupted in the lower jaw since childhood. Lips were erupted. He had sparse, thin, lightly pigmented scalp hair. There was periodical 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 endodontics. 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 two pathologies can share some facial features. A mimetic examination of acromegalic patient can reveal such underlying disease.

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P714

Sever hyponatraemia and SIADH secondary Bortezomib: case report

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Introduction

The Syndrome of Inappropriate Antidiuretic Hormone (SIADH) is considered to be the most common cause of euvoletic hyponatraemia. 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. Electrolyte 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 hyponatraemia 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 euvoletic with no neurological compromise. A blood test showed severe hyponatraemia (107 m mol/l) and she was referred to the acute medical unit for admission. A diagnosis of SIADH was made according to Barter-Schwartz criteria. Her serum osmolality was 226 m osmol/kg [275–295 mosm/kg], urine osmolality was 119 m osmol/kg [300–900 mosm/kg] and, her urine Na 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 hyponatraemia. 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 liver function was performed, which revealed hypopituitarism (Cortisol = 1.8 μg/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 on hormonal replacement therapy with hydrocortisone, thyroxin and testosterone. FT4 was 502 mIU/l, weight decreased on 19.5 kg (from 124.5 to 105 kg), BMI adherence 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/m². There were some improvements in lab parameters: glucose after 120 minutes OGTT = 7.8 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 hypothalamic-pituitary axis were excluded. Patient’s testosteron level was 1.88 mmol/L, LH = 0.24, FSH = 1.77, PRL = 7.509 mIU/L. We performed pituitary MRI, which revealed a macroadenoma 18x16x16 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 headache was in several months ago. Perimetry revealed no visual 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/m². There were some improvements in lab parameters: glucose after 120 minutes OGTT = 7.8 mmol/L, HbA1c = 6.1%, insulin = 16.2, LDL-cholesterol = 3.27 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 act 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. Pituicytic magnetic resonance imaging (MRI) revealed hypointensized lesion, 12mm in size, in right part of the pituitary gland. At the same time abdominal MRI described bilateral adrenal hyperplasia. Transphenoidal pituitary surgery was performed and ACTH secreting pituitary adenoma with Crooke’s hyaline was found on pathohistology. 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 continued 3 months follow up and patient was disease free. Six months after surgery patient had positive hormonal and MRI findings for pituitary adenoma remnant. Abdominal MRI was still unchanged. 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 supression 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 hypercortisolism due to ARMC5 mutation. So far we know that ARMC5 mutation lead to PBMAH. Recent studies have shown that the various ARMC5 isoforms are present in most of 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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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 overweighment. Maximum weight attained in adult hood was 70 kg, maximum BMI was for that moment—124.5 kg, BMI = 43.3 kg/m², 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 galactorrhoea, 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 hypothalamic-pituitary axis were excluded. Patient’s testosteron level was 1.88 mmol/L, LH = 0.24, FSH = 1.77, PRL = 7.509 mIU/L. We performed pituitary MRI, which revealed a macroadenoma 18x16x16 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 visual 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/m². There were some improvements in lab parameters: glucose after 120 minutes OGTT = 7.8 mmol/L, HbA1c = 6.1%, insulin = 16.2, LDL-cholesterol = 3.27 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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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 amenorrhoea. Pituitary MRI showed a focal anterior pituitary lesion compatible with a subacute hematoma. Clinic and laboratory examination revealed hypopituitarism: central hypothyroidism (TSH = 0.0197 uIU/mL, FT4 = 10.05 pmo/L), low IGF-1 = 21.22 ng/ml, hypocortisolism (ACTH = 19 pg/ml, cortisol in the morning (SAM) = 3.84μg/ml); hypogonadotropic hypogonadism, (PSH = 0.86 cm/L, LH = 0.23 mIU/mL, Estradiol = 10pg/ml), normal prolactin, (6.14 ng/ml), hyponatremia, 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.

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From acral 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 acral 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 with 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 cortisol: 15.0 μg/24h (4.3–176.0) and ACTH <5.0 pg/ml. Urinary metanephrine and plasmatic catecholamine levels were elevated, but less than twice the normal value. IMBG 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 expansion 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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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 hypogonadotropic hypogonadism, LH 2.3 µIU/L (2–9), FSH 0.9 µIU/L (2–12), Testosterone 1.2 µmol/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 glycaemic control was achieved with the addition of regular insulin and his acute kidney injury resolved.

Conclusion

Hypercglycemic 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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P724

Twelve years 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 unblinded 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 discontinuation. 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 Cobimetabib developing transient inflammatory like arthritis which responded to anti-inflammatory therapy and dose reduction in Vemurafenib. 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 induced hypophysitis 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
Meningoencephalitis 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 suprassellar 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 9.9 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 tumor. Immediately after surgery cortisol and free thyroid hormones levels decreased and she was discharged 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% polymorphonuclear); 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, Vancomycin and Ampicillin 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 –1.18) with weight 18.2 kg (SDS –1.36). She 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 heterogeneous 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 and testosterone, 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. 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 regardless clinical signs and a hight free urinary cortisol at 4839 nmol/l, ACTH was normal at 4.4 pmol. The retaining etiologic was a macroadenoma measured 17×11×10 mm lowering the sellar floor and optic-choiasmatic tanks with visual field impairment: presence of central scotomas and devices. Treatment consisted of a transsphenoidal resection at 13 weeks of pregnancy. 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 pregnancy was achived without maternal or fetal complications. Our second patient was 35-year-old and operated for Cushing’s disease. The indication of revision surgery for a microadenoma was interrupted 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

CNHC: 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 (SMDT) and other growth disorders. In our country, rSMT therapy is approved for isolated/multiple somatropin deficieny, small for gestational age (SGA), chronic kidney disease (CKD), Turner syndrome (TS) and Prader Willi syndrome (PWS). A National Committee (CNHC) is responsible for the analysis of each case and treatment approval.

Methods/design
We performed a retrospective and comparative study of 111 patients who completed rSMT treatment, monitored by the CNHC. 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 SMDT 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 SMDT 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 SMDT (mean SDS variation of +1.4), followed by multiple pituitary 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 1.3 cm/year; P = 0.004). 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.

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. 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/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.

Endocrine Tumours and Neoplasia

P730

The down-regulated Tumour suppressor Wnt Inhibitory Factor 1 (WIFI) 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 inhibitory factor 1 (WIFI) and the secreted frizzled-related proteins 2 and 4 (SFRP2 and 4). These results have been confirmed by qPCR and shown that WIFI is under – expressed in all tumour types while SFRP’s tend to be repressed in functional PAs. In this study, microarray analysis on locally resected PA revealed strong down-regulation Wnt pathway antagonists, namely the Wnt inhibitory factor 1 (WIFI) and the secreted frizzled-related proteins 2 and 4 (SFRP2 and 4). These results have been confirmed by qPCR and shown that WIFI 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 WIFI in PA in relation to the different Wnt signalling pathways using two established cell lines, the rat somatotroph/lactotroph GH3 and prolactinoma MMQ cell lines in the presence of known canonical and non-canonical Wnt ligands, Wnt3, Wnt4 and Wnt5a. WIFI over-expression reduced significantly GH3 and MMQ cell proliferation using a fluorescence-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 inhibitor, 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, WIFI, 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 FluoroForte 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 WIFI inhibitor. Wnt ligands activated calcium release with variable potentials with WIFI 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 WIFI could play a role in PA by inhibiting specific aspects of this pathway.
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 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-secretting GH and prolactin with a normal IGF1 level and no acromegalic features at the beginning.

Case
A 58-year-old woman 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 x 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 x 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 x 7 mm and stabilized. Cabergoline therapy was planned to be continued due to the absence of significant symptom.

Conclusion
Co-secretion is usually seen in tumors with somatotrophs and mammotrophs together, mammomatosomatomorphic 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 x 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 hypointense 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 showed bilocular cystic appearance, 12 x 13 x 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 chromosomal 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 chromosomal 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 functionally 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, FGFI13 and VEGFD 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 chromosomal insertion into aggressive lactotroph tumours only in male. If we compare transcriptomic and CGH analysis, two genes are up regulated in male lactotroph tumours and located on inserted chromosomal 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 chromosomal alterations in lactotroph pituitary tumours. The differentially expressed genes are implicated in tumour growth, invasion and malignancy and some of them is 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.

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 diagnosis 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 in 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 89% 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 SCA 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 SCA, after median follow-up of 71 months, the cure rate was 4.5% in per primam SCA and 9% in the second group (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 diagnosis 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 somatostatimorphic 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 report the effectiveness of medical treatment in restoring fertility, while managing prolactinoma. And also to illustrate the follow-up of prolactinoma during pregnancy.

Cases

The first patient was 32 years old, had galactorrhoea 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 macroprolactinoma revealed by menorrhagia and galactorrhoea, and bilateral visual acuity decrease. She was treated with bromocriptine. The third woman did not follow the instructions of making contraceptifs precautions 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 paper is to report 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 developed spaniomenorrhea. Five years later, the patient was pregnant again, and was referred to us for the follow-up, which 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 syndrome. 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 gonadial 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 colloidal cyst combined with a GH-secreting pituitary adenoma with a Ki 67 proliferative index of 9%, and MAS. The GNAS gene p.Arg210His 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 colloidal 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 (QoL). 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 craniopharyngioma (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 (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 ± 21.77 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. 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 adjustment in 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 (< −2 S.D.; > +2 S.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 ± 2.2 S.D.; 72% of patients had IGF1 between −2 S.D. and +2 S.D. 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 −2 S.D. and +2 S.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 > +2 S.D (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 < −2 S.D. with GH dose adaptation (73 patients) (dose, median, (mg/d) [Q1; Q3]).

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Table 2 IGF1 > +2 S.D. with GH dose adaptation (72 patients) (dose, median, (mg/d) [Q1; Q3]).

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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 hyperandrogenism and subtle acromegalic features (macroglossia, sleep apnea). Clinical examination showed hirsutism (Ferrimann-Gallwey score 20/34), acanthosis nigricans and mild cllitordiomegaly. 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 nmol/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.

DOI: 10.1530/endoabs.56.P742

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 it 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.

DOI: 10.1530/endoabs.56.P743
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 ≥3 mm or total when more than 50% of the sella is filled with CSF and the gland thickness is ≤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 years. 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 symptoms (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: absence of 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.

DOI: 10.1530/endoabs.56.P744

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 ≥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.

Conclusions
8101 records (5454 from males and 2647 from females) of serum sodium (mean 139.4 ± 3.1 mEq/l) evaluated in HIV-infected patients (mean age 49.0 ± 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, P = <0.0001), even after the exclusion of HyperNa group (R = −0.191, P = 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).

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.

DOI: 10.1530/endoabs.56.P745

P746
Sox 2 expression in human pituitary adenomas-correlations with pituitary function
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1Carol Davila UMPh, Department of Endocrinology, Bucharest, Romania; 2C.I. Parhon National institute of Endocrinology, Bucharest, Romania; 3Victor Babes UMPh, Timisoara, Romania.

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) prevelated at the time of the neurosurgical intervention. Tissue samples were analyzed by immunohistochemistry for pituitary hormones and Sox2 expression by the avidin-biotin-HRPAP 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 corticotropic 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.

DOI: 10.1530/endoabs.56.P746
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 ≥ 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% (13%, 24%) of cases, while in patients with cortisol level ≥ 123 nmol/l, recurrence was equal to 50% (15%, 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, adrenocorticotrophic hormone (ACTH), transsphenoidal adenomectomy, cortisol, recurrence.

DOI: 10.1530/endoabs.56.P747

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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1Clinic for Endocrinology, Diabetes Mellitus and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia; 2School of Medicine, University Belgrade, Belgrade, Serbia; 3Mother and Child Health Care Institute of Serbia ‘Dr Vukan Cupic’, Belgrade, Serbia; 4University Children’s Clinic, Tirsova, Belgrade, Serbia; 5Institute of Medical Statistics and Informatics, Belgrade, Serbia.

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 ± 1.5 years.

Methods
We investigated the metabolic status (glycaemia and insulin in OGGT, HOMA-IR, lipids, HbA1c), body composition (% fat, fat mass - FM and lean body mass – LBMI) and BMD (BMD g/cm², 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 ± 2.0 yrs). The pause in GH replacement was 2.3 ± 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 insulin in OGTT, HbA1c, cholesterol, % fat and FM showed also higher levels in TU-COGHD subgroup, but not significantly (P > 0.05). In addition, LBMI, BMD (g/cm²) 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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1Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca Granda Ospedale Maggiore Policlinico, Milan, Italy; 2Karolinska University Hospital, Stockholm, Sweden; 3Janso’s University Hospital, London, UK; 4Medisch Centrum Alkmaar, Alkmaar, Netherlands; 5Sandoz International GmbH, Holzkirchen, Germany; 6Max Planck Institute of Psychiatry, Munich, Germany.

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/m². 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® therapy; 45 (40.9%) were related to rhGH treatment 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/m². 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® therapy; 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.

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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 Trifunovic¹, Branka Sošić-Jurjević², Milica Manojlović-Štojanoski², Nataša Ristić², Nataša Nestorović², Branki Filipović² & Verica Milošević²

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The different response of somatotropic system to genistein and daidzein in the rat hypothalamus: Svetlana Trifunovic, Branka Sošić-Jurjević, Milica Manojlović-Štojanoski, Nataša Ristić, Nataša Nestorović, Branki Filipović, Verica Milošević

University of Belgrade, Institute for Biological Research ‘Sinisa Stankovic’, 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 have 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 have 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 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. 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 combined 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 transsphenoidal 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 SSTR2 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 sex-normalized) and stability of residual tumor mass at radiological evaluation. None of patients had significant adverse effects, particularly worsening of glycomic 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.

DOI: 10.1530/endoabs.56.P751
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 sinus invasion or signs of nerve compression.

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P753

Could predict the postoperative resonance 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 13 patients treated preoperatively with PPS, 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 MRI were 10.50 ± 0.73 ng/dl, IGF-1 1754 ± 98.97 and Nadir GH 1.69 ± 0.23 ng/dl, in anormal MRI were 7.29 ± 8.11, 576.19 ± 295.76 and 7.02 ± 6.36 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 approved 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 obstruction 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 >3.1 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 5.5 (2.74) from baseline. 72/33 (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<0.001 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 Rocío 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 [IQR: 25-46.60]. 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 in Ki67 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 abscess 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 lesions. 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% (3) 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±1.5 years. All of them were submitted to transsphenoidal 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.

Conclusions

We describe a large cohort of patients compared to the reported cases in the scientific literature. We observed a high cure rate in our series, 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. We studied 85 patients with hormonally inactive pituitary adenomas, 45 women and 40 men 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 macroadomas hyperprolactinemia was clinically presented in combination with hypopituitarism. Among patients of the third group, chiasmal and cephalic syndromes, the latter with the oculomotor nerve damage, were the main symptoms; lactorrhea-ameneroeha 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 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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Subject BMI and FMI did not change. Also, the proportion of subjects with either femur neck, and total body, as well as FFMI increased over time, while SDS for BMD reflected by negative mean values for SDS for BMD. SDS for BMD of L2-L4, K, K, n, K, K, 0.93–5.02, n, Z, 4.21–2.40, n, 72, mean SDS for femur neck was −0.60 (range −4.53–3.80, 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 BMI 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 BMI and FMI, and of decreased bone health, reflected by negative mean values for SDS for BMD. SDS for BMI for 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 hypothalamic-pituitary-adrenal axis insufficiency. Adrenocortical insufficiency is especially worrisome given its potentially life-threatening course, if untreated. Usual clinical practice includes administration of periprostatic “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 collected, 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% craniopharyngiomas, 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

P0.99 [95%CI 0.54-1.44; difference 0.80 [95%CI 0.28-1.18; 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 BMI and FMI, and of decreased bone health, reflected by negative mean values for SDS for BMD. SDS for BMI for 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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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 eradication of the tumor), allowing discontinuation of treatment. So far, there are neither clinical criteria with sufficient predictive value for long-term remission.

Objective

To assess the effect of DA withdrawal, the current recurrence of hyperprolactinemia, and possible 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 disease signs or symptoms. The most frequent indicator of recurrence was asymptomatic hyperprolactinemia (85%).

Table 1 Data of the remission and recurrence groups about sex, sellar adenoma, microprolactinoma and tumoral mass reduction.

| SEX (FEMALE) | 9/9 (100%) | 6/7 (85.7%) | ns |
| SELLOAR ADENOMA | 7/9 (77.7%) | 5/7 (71.4%) |
| MICROPROLACTINOMA | 7/9 (77.7%) | 5/7 (71.4%) |
| TUMORAL MASS | 3/9 (33.3%) | 4/7 (57.1%) |
| REDUCTION >20% | |

Table 2 Data of the remission group about age at diagnosis, baseline PRL levels, PRL levels after treatment, treatment dose and adenoma diameter.

<table>
<thead>
<tr>
<th>Remission group</th>
<th></th>
<th>Recurrence group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis (years)</strong></td>
<td>35.47</td>
<td>25.62</td>
<td>4.12</td>
</tr>
<tr>
<td><strong>Baseline PRL levels (ng/dl)</strong></td>
<td>214.94</td>
<td>209.94</td>
<td>41</td>
</tr>
<tr>
<td><strong>PRL levels after treatment (ng/dl)</strong></td>
<td>14.92</td>
<td>12.74</td>
<td>21.70</td>
</tr>
<tr>
<td><strong>Initial treatment dose (mg/week)</strong></td>
<td>6.28</td>
<td>7.71</td>
<td>2.41</td>
</tr>
<tr>
<td><strong>Adenoma diameter (mm)</strong></td>
<td>7.74</td>
<td>2.81</td>
<td>10.42</td>
</tr>
<tr>
<td><strong>Time to treatment withdrawal (months)</strong></td>
<td>36.12</td>
<td>25.62</td>
<td>18.71</td>
</tr>
</tbody>
</table>
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 macroadenoma: 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 imaging scan of the brain showed a 45.5×50 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 irregula
dy, 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 partial 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 16.8 ug/dl. 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, optic nerve decompression, plasty of bone sellar region. Results: CABG were restarted (1.5 mg/week). During the first admission, no statistically significant differences were found between patients with pre- and postoperative central DI (P > 0.05). When assessing the level of copeptin, there were no statistically significant differences in the level of osmolality and sodium in patients with a constant and transient form of central DI compared to patients with transient (P > 0.008) and permanent form of DI (P < 0.05). 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 compared to patients with transient without disturbances (P < 0.05), and significant differences in the level of osmolality of urine in the dynamics of 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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Objective
To assess the levels of osmolality, sodium and copeptin as predictors of the development of postoperative diabetes insipidus

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Materials and methods
A total of 154 patients, aged 18 to 65 years, were included in this study and underwent transsphenoidal adenomectomy for pituitary adenomas.

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 hypopituitarism 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 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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P765

Rathke's cleft cyst mimicking 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 woman was referred to the emergency room for sudden headache and fatigue without visual disturbance. Neurological examination was normal with normal limits and brain CT showed a high density 9 mm area in the sella suggesting a pituitary apoplexy. The patient was hospitalized and treated with hydrocortisone infusion. Hormonal profile was within normal limits indicating normal pituitary function. On MRI study, oval slightly hypointense 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 (IGF-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 in 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 acromegaly 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, IGF-1, GR, register, AcroQoL.
DOI: 10.1530/endoabs.56.P766

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 had regular menstrual cycles, 147 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 remission, 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 (92.6%) patients received drugs for control cortisol hypersecretion; all 25 received Ketoconazol, in the other 2 (7.41%) the treatment (ketoconazol) was discontinued due to hypertensaminemia. Median presurgical dosage was 600 [400-600] mg/día. 8 (29.6%) patients were macroadenomas 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 approach. 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 insipidus, 2 (10.53%) patients thyroid dysfunction, 11 (57.89%) steroid dysfunction and 1 (5.26%) gonadal one. 1 patient showed presurgical campyromet defects which showed an improvement after de surgery. 8 patients operated in this period had been operated previously via transsphenoidal microscopic. At the end of the observation period 6 (75%) patients were disease-free. 1 complications after surgery in reoperated patients, 1 patient showed a suspected meningitis and hydrocefealus. 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 microsurgical approach if we compare our series with the literature and no further complications were found. ETPS is shown as a very useful technique in patients previously operated by a microsurgical approach. DOI: 10.1530/endoabs.56.P768

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 surgically removed via ETPS between January/2013 to January/2017.

Results
Among 67 patients with non-functioning pituitary adenomas surgically removed via ETPS (44 (65.67%) were men. 52 (77.61%) patients received 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 transssephoidal 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%), steroid dysfunction, 41 (62.12%) gonadal dysfunction and 25 (37.88%) somatotrophic 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-67%. Median uterine size was 27 [21.7-33.7] mm, 45 (67.16%) showed a size >25 mm and 29 (43.28%) Knos 3-4. 52 (77.61%) were operated by first time. 36 (53.93%) 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 patient with tumors remain >1 cm were adenomas >25 mm, 10 (90.9%) showed cavernous sinus invasion. 33 (63.46%) showed presurgical campyromet defects; 21 (63.63%) resolved completely their campyromet defects, 10 (30.3%) showed a partial resolution and no changes were found in 2 (6.06%) patients. After surgery, transient diabetes insipidus 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 campyromet defects, after surgery 1 (14.29%) resolved completely their campyromet defects, 6 (85.71%) showed an improvement. After surgery, among patients without endocrine involve, 3 (42.86%) presented thyroid deficiency, 3 (33.33%) steroid, 1 (25%) gonadal deficiency.

Conclusions
In our series, ETPS have shown better outcomes than transssephoidal microscopic approach if we compare our series with the literature. This approach leads to complete curetion in patients with sinus involvement. DOI: 10.1530/endoabs.56.P769

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. DOI: 10.1530/endoabs.56.P770

Paediatric Endocrinology

P771
Therapeutic results of growth hormone substitution in children monitored for a growth hormone deficiency: 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 chronological 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.
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 GH 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 GH 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

<table>
<thead>
<tr>
<th>Characteristics of the patients</th>
<th>IGHD at diagnosis (n=22)</th>
<th>GHS in transition (n=7)</th>
<th>GHS in transition (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>9.6 (2.8)</td>
<td>8.6 (3.1)</td>
<td>10.1 (2.6)</td>
</tr>
<tr>
<td>Sex (M: F)</td>
<td>15:7</td>
<td>5:2</td>
<td>10:5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>127.9 (13.1)</td>
<td>120.5 (12.3)</td>
<td>131.5 (13.1)</td>
</tr>
<tr>
<td>Target height (cm)</td>
<td>168.6 (6.8)</td>
<td>167.9 (6.7)</td>
<td>166.5 (7.1)</td>
</tr>
<tr>
<td>GH peaks at diagnosis 1st test</td>
<td>5.79 (2.7)</td>
<td>6.3 (2.6)</td>
<td>5.5 (2.8)</td>
</tr>
<tr>
<td>2nd test</td>
<td>5.12 (2.5)</td>
<td>5.1 (2.3)</td>
<td>5.1 (2.6)</td>
</tr>
<tr>
<td>&lt; 5 ng/ml</td>
<td>0</td>
<td>0</td>
<td>9 (1.6)</td>
</tr>
<tr>
<td>5–10 ng/ml</td>
<td>1st test: 10</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>10–15 ng/ml</td>
<td>2nd test: 9</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>&gt; 15 ng/ml</td>
<td>1st test: 12</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Age at the GH re-evaluation (years)</td>
<td>16.1 (1.4)</td>
<td>16.5 (1.8)</td>
<td>15.8 (1.3)</td>
</tr>
<tr>
<td>GH peak at the end of GHRx (ng/ml)</td>
<td>7.3 (3.6)</td>
<td>2.8 (1.4)</td>
<td>9.3 (2.6)</td>
</tr>
<tr>
<td>Height at the end of GHRx (cm)</td>
<td>162.8 (9)</td>
<td>163.4 (11.7)</td>
<td>162.5 (8.1)</td>
</tr>
</tbody>
</table>

*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 chromosome 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 redetermination ( −2 SD). Height was at 25th centile, weight at 5th 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, 17βestradiol, 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 (IGHD) and precocious puberty.Therapy with Triptorelin and rhGH was prescribed. After six months,

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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, 63.6% male. The median age at cancer diagnosis was 5.6 years and 60.7% had central nervous system tumors; 60.7% underwent surgery, 71.4% radiotherapy and 67.9% chemotherapy. Only 42.9% had IGF1 more than 2 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<0.001). 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<0.001). 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 not 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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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 at a mean of 19.5 years prior to pregnancy. The cause of hypopituitarism was pituitary agenesis in two patients, macroadenoma 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 GmRH 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 cesarean 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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P777
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 magnetofection, 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

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was detected between the treated and untreated wtAHR (P = 0.021), Arg554Lys (P = 0.005) and Val570Le (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 suggested that this mutation is quite rare and may be similar to the frequencies of other European populations.

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 transphenoidal surgery. From fresh frozen tissues DNA extraction was performed using QIAamp Fast DNA Tissue Kit. For library preparation Enzymatic Amplification Mitochondrion Preparation 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 ± s.e.) reads per base. 496 variants were identified in adenomas compared to reference sequence. Overall a low (7.22%) heteroplasmasy 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, 0.0142, 0.0246 and 0.01829, respectively). Of these variants chrM_14798 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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P778
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 indicated 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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P797
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 transphenoidal surgery. From fresh frozen tissues DNA extraction was performed using QIAamp Fast DNA Tissue Kit. For library preparation Enzymatic Amplification Mitochondrion Preparation 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 ± s.e.) reads per base. 496 variants were identified in adenomas compared to reference sequence. Overall a low (7.22%) heteroplasmasy 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, 0.0142, 0.0246 and 0.01829, respectively). Of these variants chrM_14798 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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P778
Pituitary cell activation and recruitment in hypothyroidism
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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 in pathological physiological 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 establishment 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 cycloamine, 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 an 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/PTSH+ 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...
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 overexpression of SF1 has been reported in adrenocortical tumours.

Aim of the study
To identify factors associated with SF1 gene expression in NFPAs.

Material and methods
Twenty-nine NFPAs (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 ILH expression (r = 0.77, P < 0.0001 in the whole series, r = 0.71, P = 0.0001 in Gn-PA) whereas correlations with βFSH only approached significance (r = 0.57, P = 0.0502 in the whole series, r = ns in Gn-PA). A positive correlation was also observed between SF1 and AIP (r = 0.52, P = 0.0038 in the whole series, r = 0.47, P = 0.023 in Gn-PA) and in particular with D2R expression (r = 0.67, P < 0.0001 in the whole series, r = 0.56, P = 0.007 in Gn-PA).

Conclusion
SF1 is a marker of gonadotroph differentiation in NFPAs and its expression is significantly correlated with ILH, 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 NFPAs 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 (CFA) 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 CFA 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 CFA 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.

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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 NURR7 (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), RGSL1 (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 ALX2CL (FC = 4.1) and TRIP5B (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 RAB3C and TRIP5B suggests that they have different stimulatory effects 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 disease development.

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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 secrete hormones in response to physiological needs.

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 gonadotrophs, are characterized by high genomic instability.

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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-secreting 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 GFP+ mammomatomatosa 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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Activation of pituitary stem cells modulated through 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 pituitary 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 constitutively-active form of YAP in the pituitary does not lead to tumour formation, revealing that YAP activity 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 reinitiate their activation. Together, our 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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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 hypogonadotrophic 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. Somatomeric 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 pituitary gland. 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.

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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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 anterior pituitary 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 hypogonadotrophic hypogonadism and adrenal insufficiency, while 79 (98.8%) patients had secondary hypothyroidism. Somatotroph function was investigated in only seven patients and was deficient in all of them. The mean BMI was 26.55±5.04 kg/m². 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).

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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 GH deficiency 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 (11.967971) 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 AGHD (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 (HSDS) and insulin-like growth factor-I (IGF-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 (0.09)) 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 SDS) at baseline (~ 2.97 (0.91)) (GHD), ~ 2.55 (1.10), TS, ~ 2.66 (0.93), NS, ~ 2.83 (1.13). HSDS was greatest in year 1 (baseline to near adult height): 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 SDS from baseline at year 1): female, 1.20 (1.51), male, 1.52 (1.47). Safety: no new serious signals were observed. Number of events/number of patients were: paediatric, NSARs, 288/249; SARs, 133/90; SAEs, 352/224; adults, NSARs, 695/24; SARs, 38/29; SAEs, 200/19.

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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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 52-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 suprasellar 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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P791

Relationship between cortisol increment and basal cortisol: implications for the insulin tolerance test in assessing corticotropic 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 > 200ng/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 (60th min, P < 0.05). 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 < 0.05).

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 insufficiency under ITT.

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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 (β: 0.34 P < 0.001, and β: 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) 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 SES 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 55.5 ± 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 ≤ 0.001). There was a significant positive correlation between Anti-TPO and Anti-TG and empty sella syndrome (r = 0.65, P ≤ 0.001, r = 0.63, P ≤ 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 ≥ 10.5, the sensitivity was 80% and the specificity was 79%. The AUC value of Anti-TPO was 87.9% (P ≤ 0.001) and the AUC value of Anti-TG was 86.4% (P ≤ 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 macroadenomas (non-gPRLomas).

Patients and methods

A retrospective and multicenter study of gPRLomas in men and to compare them with those of a group of male patients with non-gPRL macroadenomas (non-gPRLomas).

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 without radiological evidence of pituitary tumor) was achieved in 2 (8.7%) gPRLoma patients and in 2 (4.8%) non-gPRLoma patients (NS).

Conclusions

Giant prolactinomas 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 = 0.001) 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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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 meningionas 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 showed 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 levels – 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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Thyroid autoimmunity and euthyroid hashimoto thyroiditis frequency in patients with pituitary adenoma

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Purpose

The purpose of this study was 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 = 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 ≤ 0.05). Anti-TG (P = 0.011) and Anti-TPO (P ≤ 0.001) values were significantly higher in patients with pituitary adenoma compared to healthy subjects values. Anti-TPO and Anti-TG positivity was detected in 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%, 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 = 0.216; P = 0.001) and Anti-Tg (r = 0.338; P ≤ 0.001) 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 ≤ 0.001).

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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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 cabergoline. 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 amenohorea. The pregnancy test was negative and pelvic ultrasound demonstrated enlarged ovaries with multiple cysts. The case was treated with GnRH agonist by gynecologist, but and the ovaries remain hyper stimulated and amenorrhea. 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; Prolactin 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 35×20×25 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 gonadotrope 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 multicyclic 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 other 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 hypothryoidism. The Insulin 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 adrenocortical deficiency 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%. Hypophyysial 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 mg/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 hypothryoidism. 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, polydipsia, 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 U/l/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 = 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
Diabetes 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 hypothryoidism, 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 insipids 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.

Objective
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.

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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 pg/ml. 85.7% had normal derkematone 1 mg suppression test, 71.4% positive 8 mg suppression 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%, 1st line Treatment: 100% underwent TSS (transsphenoidal surgery). The remission, recurrence and persistence rate were: 36.4%, 36.4% and 27.3% respectively. Remission rate after “normal anathomopathology” was 57.1%. Remission rates: in patients <30 years old remission rate was 12.5% vs >30 years 50%, micro 47.7% vs macro 33.3%,women 43.8% vs men 16.7%, early posturgy 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. 79% had “normal conventional RM” and were diagnosed with ‘3T RM/metionin PET, 69.2% underwent second TSS and 30.8% radiotherapy. Remission, recurrence and persistence rate after second line treatment were: 50%, 71% and 42.9% respectively. After all treatments 68.2% are cured (13.3% with panhypopituitarism)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 postsurgery 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 macroadenoma**

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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 macroadenoma. After 3 months of CAB treatment, PRL normalization was achieved in 109 (88.6%) of macroadenoma 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 ≤5, n=82) and high normal group (5 <PRL ≤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 ≤1, n=49) and high normal group (1 <PRL ≤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±13.87%, P=0.014). Even if we narrow down the high normal group (1 <PRL ≤10, n=50) and 1<PRL ≤5, n=33), similar results came back (27.18±18.31 vs. 19.30±13.66%, P=0.017 and 27.18±18.31 vs. 19.22±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 patient had recurrence (3/34 patients, 8.8%). The size of the adenoma 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 5%, 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 ≥5% 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=0.008 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 adenoma had significantly higher expression of Ki-67 than 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 hypophalamo-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 hypophalamo-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 subjects (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 (NFPPAs) 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 NFPPAs during 2011–2016 with available preoperative combined pituitary function test (CPTF) 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 NFPPAs. 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 sela magnetic resonance imaging (32.4 vs. 9.2%, P < 0.001) were higher in the SCA group. In the preoperative CPTF, 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 ± 46.51 vs. 107.66 ± 86.05 pg/mL, P = 0.001) were significantly lower in SCAs. Female sex, cavernous sinus invasion, intra-tumoural haemorrhage on sela 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 hypergonadotropic hypogonadism the low testosterone levels are a result of insufficient gonadotropin levels. Hyperprolactinemia is a cause of hypergonadotropic 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 parasellar sinus (pituitary mass with 23 × 15 × 13 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/d, spironolactone 25 mg/d 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 UI/L (1.5–12.9 UI/L), LH 6.83 UI/L (1.3–9.8 UI/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/mL, 6 months after the switch) and tumor size reduction (absence of supra-sellar extension 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 UI/L and LH 12.8 UI/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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**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 acromegaly 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 acromegaly 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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**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 B/I/ml, range: 0–157) is found elevated while antimicrosomal antibodies was negative. Thyroid gland had a heterogeneous echotexture on the ultrasoundography. 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 ophthalmology outpatient clinic with a 2 month history of loss of vision at left eye and blurred vision at right also headache and fatigue. Ophthalmological 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 panhypopituitarism. Pituitary MR imaging demonstrated contrast enhancing mass lesion at suprasellar cisternal region which outstrecthed to posterior perimesencephalic cisternal region. The mass resected by craniotomy was a germinoma. Histopathologic examination showed germinoma. Chemotherapy and radiation therapy were administered. He is still using prednisonol, t-xyroxine and human chorionic gonadotropin treatment.

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P816

Primary pituitary absciss: an unexpected diagnosis

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Pituitary absciss is a rare condition, with approximately 200 cases reported in the literature. Two-thirds of pituitary absciss which occurs without any of the aforementioned risk factors is primary type while remaining are secondary type-absciss. 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 postrolateral. 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 meronidazole,ceftriaxone and linezolid for 2 weeks and 4 weeks of meronidazole, ceftriaxone and sulfamethoxazole/trimethoprim. Her headache, fatigue, loss of appetite resolved. After surgery hypopituitarism continued and treated with oral prednisonol and t-xyroxine 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, the pathogenetic and prognostic significance of pineal disorders in neoplastic disease showed germinoma. Chemotherapy and radiation therapy were administered. He is still using prednisonol, t-xyroxine and human chorionic gonadotropin treatment.

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

An abnormally high serum levels of MT at the period of maximum light and abnormally low increases during the night were seen in 31/52 ACRO (GH 23.6± 24.9, Me = 14.0 [3.1–44.9 ng/l]) and 12/17 PROL (PRL = 248.5± 55.4, 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 Mtn 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 = 0.001; Mtn – 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), MT levels 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 hypothalamic and infundibulo-neurohypophyseal dysfunction

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Autoimmune hypothalamin 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 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, testosteron, normal cortisol levels, but thyroid hormone levels were in the normal range with high TSH and anti-TPO levels. Response to LRH 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. Poluyama improved after oral administration of desmopressin 2×120 μg. We did not give steroid treatment, levotyroxin was administered for the subclinical hypothyroidism. The symptoms improved in six months without steroid treatment, anterior pituitary functions returned to 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. Poluyama improved after oral administration of desmopressin 2×120 μg. We did not give steroid treatment, levotyroxin 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 microscopical involvement of anterior pituitary. He is still being followed with desmopressin and levotyroxin. As far as we know this is the first case of hypothalamin and infundibulo-neurohypophyseal dysfunction with symptoms of DI and partial hypopituitarism. To conclude, in a patient presenting with headache, hypopituitarism and a suprasellar mass, hypothalamin also should be considered in diferential diagnosis. Because it is a self-limiting condition, close follow-up with clinical and laboratory testing can be

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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 (VF)s 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 thyroidropin (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 VF s 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 VF s using a morphometric approach on lateral chest X-ray routinely performed in the pre-surgical diagnostic work-up.

Results
At the time of VF assessment, 17 patients (77.3%) had an overt hyperthyroidism and five patients (22.7%) had thyroid hormone values in the reference ranges. At the time of VF assessment, 17 patients (77.3%) had an overt hyperthyroidism and five patients (22.7%) had thyroid hormone values in the reference ranges. VF s 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 VF s 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 VF s 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

Results
49 patients with CD. Age 44.4±15.29 years. Women: 89.8%. Transsphenoidal surgery: 87.8%. Remission: 68.7%. Time from onset of clinical to diagnosis: 29.7±27.30 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.

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 an 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 accumulation 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 = 0.003). 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). Hypopituitary 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 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 FT4 and FT3 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, FT4, FT3, 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; FT4, 11.5–22.7 pmol/l; FT3, 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 thyrostaticus (four cases). Hyperthyroidism symptoms were observed in 16 (76%) patients. The level of TSH was 2.47–38.4 mIU/l (median, 6.56); FT4, 22.8–54.8 nmol/l (median, 36); FT3, 3.5–6.5 pmol/l. An immunohistochemical 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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P824

Hypothalamic involvement in diffuse large B-cell lymphoma

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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, hypothalamic 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. 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 (rituximab, methotrexate) and cranial radiotherapy. During hospitalization, hypotension, polydipsia, polyuria were observed. Hormonal and clinical evaluation was compatible with central diabetes insipidus and panhypopituitarism. 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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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 cosyntropin 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±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 recurrence time of adrenal function represented a significant predictor for persistent remission (OR: 1.14, CI: 1.003–10.3, 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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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 asphyxiation/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 psychotherapist, 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 pituitary 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 macro adenoma, 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 headache within 24 h after steroids treatment. After five days of hydrocortisone treatment l-thyroxine 25 μg/day treatment was given for secondary hypothyroidism 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On admission</th>
<th>6 months after delivery</th>
<th>Normal reference value</th>
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<tbody>
<tr>
<td>ST4 (pmol/l)</td>
<td>9.0</td>
<td>16.5</td>
<td>12–22</td>
</tr>
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<td>TSH (mU/l)</td>
<td>0.064</td>
<td>0.151</td>
<td>0.4–4.2</td>
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<td>PRL (ng/ml)</td>
<td>352</td>
<td>467</td>
<td>4.7–23</td>
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<td>GH (ng/ml)</td>
<td>0.187</td>
<td>0.675</td>
<td>0.4–3.0</td>
</tr>
<tr>
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<td>287</td>
<td>116–358</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>175</td>
<td>138</td>
<td>171–536</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
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<td>&lt;5</td>
<td>0–46</td>
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<tr>
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<td>&lt;0.1</td>
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</tr>
<tr>
<td>LH (IU/l)</td>
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</tbody>
</table>

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P827

Benefits of pre-surgical treatment with somatostatin analogs in naïve 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).

Objective
To evaluate the effect of first-generation SS-analogs (lanreotide and octreotide) on tumour shrinkage and biochemical control in naïve 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 glicaeic 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 macro adenomas. BMI was 26 ± 4 kg/m². Hypertension was found in 47%, glicaeic 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 ± 2 previous vs 15 ± 9 mm, P = 0.001), TV (3098 ± 4829 vs 2362 ± 5005 mm³, 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 ± 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 glicaeic metabolism after receiving treatment with SS-analogs (glycemia 119 ± 37 vs 114 ± 17 mg/dl, P = 0.74 and HbA1c ± 0.9 vs 6 ± 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 achT-staining pituitary tumors

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Background
Temozolomide is an alkylating chemotherapeutic 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 significant 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 capcetabine. 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 hypercortisolism. 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 capcetabine) 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/IGF1, 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 55 ± 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-1 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 ± 24 years, and the types of cancer were: in two men lymphoma and lung cancer; in two women rhabdomyosarcoma in mediastium 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-1 level is rarely diagnosed and is difficult to recognize. In acromegalic pa-tients with poorly controlled diabetes, malnutrition, hepatic injury, hepatic congestion due to heart failure, 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 cranio-pharyngioma. 28 years ago the patient had undergone partial thyroidec-tomy 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 osteosarticular 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 mg/ml, n: <0.4). IGF-1 = 157.3 mg/ml (n: 29–204). The remaining pituitary functions were normal. On the basis of OGTT (96 mg/ml~150 mg/ml) an impaired glucose tolerance was diagnosed. In MRI pituitary tumor 17 × 19 × 14 mm was detected. Renal insufficiency, malnutrition [BMI = 34.2 kg/m²] 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 acromegals 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 acquired by dual X-ray absorptiometry (DEXA). At trabecular level, GH may alter bone microarchitecture (BM) that predisposes to bone fragility.

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 DAX 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. DEXA 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/m²) and 128 control subjects (53.1% women; age 50.9 ±20.3 and median BMI 24.9 kg/m²) were evaluated. TBS was lower in patients compared with control (t 1.26 ±0.13 vs. 1.35 ±0.18; P=0.01), with no significant differences in BMD (g/cm²), 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, particularly 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. The prevalence in Moscow city which represents a multinational population was 4,5% per 100 000 population. The prevalence in Moscow city which represents a multinational population was 4,5% per 100 000 population.

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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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, extended 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 suppression test were within normal range and physical examination did not show any cushingoid signs. Transnasal transsphenoidal surgery was performed and pathology reported as “densely granulated corticotroph adenoma, Ki 67: %3, p53 (+)”. After first evaluation he underwent to brain MRI that revealed pituitary adenoma about 12x9x5mm 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 suppression tests were in normal range, patient had also no cushingoid signs. Transnasal transsphenoidal surgery was performed and pathologic examination revealed “corticotroph staining adenoma as Ki 67: %2 and p53 (+)”. 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.

A 55 years old male admitted to hospital with a complaint of headache. Past medical history includes prior pituitary surgery, depression and hypertension. His medical history includes prior pituitary surgery, depression and hypertension. His medical history includes prior pituitary surgery, depression and hypertension. An MRI of the sella was performed and pituitary mass was detected 20x16x15x10mm diametered, heterogeneous in nature, extended to suprasellar region, infiltrates cavernous sinuses and contact with optic chiasma. Cushing disease were 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.

P836
Early post-surgery cortisol after transsphenoidal surgery to predict adrenal insufficiency one year post-surgery
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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 3rd postoperative 0800 a.m. cortisol(after 24 without corticoids) and cortisol/Synachten 3-6 months post-surgery. We excluded patients with previous diagnosed and treated adrenal insufficiency. 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 1/3rd day cortisol lower than 15 we maintained glucocorticoid treatment until reevaluation with cortisol/Synachten 6 months post-surgery. In patients with 1/3rd 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 1/3rd day cortisol > 15mcg/dL had normal cortisol/Synachten 6 months post-surgery vs 20% of patients with 1/3rd day cortisol < 15 (P<0.05). After one year of surgery: 88.2% of patients with 1a/3rd day cortisol >15mcg/dL had adrenal sufficiency, 40% of patients with 1a/3rd 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. 4.2% 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 3rd day cortisol < 5mcg/dL are in remission 1 year after surgery vs 33.3% of patients with 3rd day cortisol > 5mcg/dL (P<0.05)

Conclusion
A 3rd day post-TSS cortisol > 15mcg/dL is a safe cut off to discharge adrenal insufficiency. 100% of patients with 3rd 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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When pituitary MRI show a typical imaging of adenoma, it is agreed that transphenoidal 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 Cushing’s disease (CD) 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 proposed and discussed in the literature, but is not widely used in clinical practice.

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 anti-diabetic 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 transphenoidal 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 cortisol levels are extremely high, the duration of symptoms is short and the clinical phenotype is different from CD. 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 differential diagnosis between ectopic 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 acausal 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±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 hypertriglyceridaemia 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 transphenoidal 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 transphenoidal 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 transphenoidal adenectomy 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. KIF-1 was 25.6±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 ≥ 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 patients 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 ≥ 0.35 cm³/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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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.

Materials and methods
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 and PL were significantly low in 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.

Introduction
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 5.6–15% 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 2300. For transcranial removal of CF we use different combinations of basal and transcavolosal 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 endoscopically). 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 transcranial surgery does not exceed 8%, after transsphenoidal 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 papilomatous 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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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 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 rheumatopaties 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 treatment, 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 analysis 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 deficit, the screening and eventually a therapeutic supplementation.

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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 craniohypangiroma.

Material and methods
89 patients (18–65 years old, mean age 38±2.44 men and 45 women) were examined after removal of craniohypangiromas in the early postoperative period. Methods: psychopathological, data from endocrinological, neurological, neuroimagining 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%) craniohypangiromas. Group 2 – 46 patients (52%) with normal serum sodium concentration after removal: endo-suprasellar (39%), suprasellar (37%), extra-intraventricular (11%) and intraventricular (13%) craniohypangiromas. 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 craniohypangiromas.

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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 ACR 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 hemorrhoids were the most frequent 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 IgF1 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 polypl (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 adherence 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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The Secret of the Ophthalmpathy

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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. Cervical bone 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 initiated 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 hyponovolemic status and hepatic dysfunction were excluded from the study. All patients received 7.5 mg/day of tolvaptan in euvolemic hyponatremic patients with SIADH.

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, NordNet 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-naive, 68.5%. Mean (SD) treatment duration, 3.1 (2.6) years. GH dose (µg/kg/day), during treatment, 46.0 (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, 2/1, SARs, 2/1, SAEs, 6/5. Most patients with AEs reported one event (16/21). For patients with SARs, 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 RA/SOPathies.

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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 Cerrahpaşa Medical Faculty were evaluated retrospectively. Clinical, endocrinological, pathological and radiological findings and therapies were assessed.

Results
Twenty patients (FM: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 Cheste disease. From 7 histologically diagnosed patients with primary hypophysitis, 5(25%) had lymphotic, 1(5%) had lymphotic-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 hypophysitis bright spot on T1 imaging (20%) and partial empty sella (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

Results
We identified 49 patients (33 P16 M), with onset age 18 (15–19) years, median (25th–75th percentile): 27 prolactinomas (5 micro, 20 macro, 2 giant adenomas [>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 mesoaedonoma, 1 macroadenoma), 1 giant GH co-secreting, thyropituitary. From 34 patients tested, two (both with giantism) had AIP mutations: c.940C>T (M-18yrs.), c.895dup (F-13yrs.). One patient with prolactinoma and primary hyperparathyroidism had MEN1 mutation: c.1449delC. Therapy included Dopamine agonists (DA): 27 prolactinomas, 8 somatotropinomas, 2 corticotropinomas, 1 NFPA, 1 thyrotropinoma; Some patients analogues: 1 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<0.001) 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-90-R, Beck Depression Inventory II (BDI-II), State Trait Anxiety Inventory (STAI) and neuroendocrine 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 Symptom Total P<0.001). 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: R=0.027, R=0.521, STAI-Trait: R=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: R=0.038, R=0.521, Depression: R=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. Secondary 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 being operated to be cured of colorectal adenocarcinoma. The patient noticed gradual enlarging of his hands, feet, lips, and nose for 30 years, but never consulted to any clinic 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 I (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), and luteinizing 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. Adrenocortical function was normal. The performance of dynamic hormone testing was below normal range (ghrelin, normally >0.15 ng/ml). 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 should not have 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 biolgical 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, and 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 (β=0.8087; P=0.0315), and acylated ghrelin concentration was significantly associated with fasting insulin concentration (β=−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 (corticotropin, thyreotropin or gonadotropin). 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 corticotropin, thyreotropin and gonadotropin was present in 17%, 17%, and 15% of patients, respectively. According to our results, every fourth patient with PES has at least 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 administra-
tion. 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 tmax 24–
97 hours) followed by a slow decay with a half-life suitable for once-monthly
dosing. Across the pasireotide sc depot dose range, AUCinf increased dose
proportionally and Cmax slightly more than dose proportionally. AUCinf and Cmax
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 transfer-
ase [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 sc formulations.

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P858

Consensus on the management of acromegaly in Spain
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Investigación Germans Trias, Badalona, Spain; 6Universitat Autònoma de Barcelona, Barcelona, Spain.

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 endocrinologists 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 recommen-
dations.

Results
The recommendations cover different aspects of clinical practice including:
1) Useful instruments for the individualization of treatment (predictive makers 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 recommen-
dations 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 recommendations 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 11β-hydroxylation of 11-deoxycorticisol, 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 transphenoidal surgery (TSS), are eligible if they have at least three baseline 24 h Urinary Free Cortisol (UFC) values that are at least 50% above the upper limit of normal (ULN = 165 nmol/24 h). Metyrapone given four or five 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-deoxycorticisol, 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 not normalized, and 6 for toxicity. Fifteen completed the 9 months therapy period. Mean reduction of UFC, eucortisolemia, clinical and biochemical improvements, will be estimated. Exploratory objectives include factors predicting success and response relationships. Results
We enrolled 30 consecutive patients (age 47 ± 12 years) referred to our Center to undergo Synacthen test (1 or 250 G). 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. Rediprol was used for R2 stimulation. 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 ≤ 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-naive 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/24 h (142–10,920). Thirty-six-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.

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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. AEIs were frequent but manageable for most patients, with <20% discontinuing because of AEs.

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 yrs) 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 to 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.

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
Cushing’s disease (CD) patients, for whom surgery has failed or is not an option, are being treated with pasireotide. The aim of this non-interventional, observational, single-arm, open-label study was to evaluate the long-term safety and efficacy of pasireotide sc in CD patients who had failed surgery. Pasireotide was started before (prior-use) or at (new-use) study entry.

Material and methods
Samples from 142 surgically resected PA were studied immunohistochemically using antisera for six 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
GH-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%) for prolactinoma and 11% (2/18) mixed GH-PRL. TSH, PRL and ACTH exclusive immunoreactivity were found in one case each. Most tumors immunopositive for GH (28/37), GH and PRL (13/18) and prolactinoma (8/13) were positive for reticulin, while those positive for PRL (9/23), ACTH (1/2), FSH-LH (7/18) and null-cell adenomas (14/50) 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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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%) for prolactinoma and 11% (2/18) mixed GH-PRL. TSH, PRL and ACTH exclusive immunoreactivity were found in one case each. Most tumors immunopositive for GH (28/37), GH and PRL (13/18) and prolactinoma (8/13) were positive for reticulin, while those positive for PRL (9/23), ACTH (1/2), FSH-LH (7/18) and null-cell adenomas (14/50) 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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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 production.

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 sinusues 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 pituitary corticotroph adenoma was confirmed using the 10% criterion in 19 patients with Cushing’s disease and correctly identified 2 patients with ectopic disease. A pituitary corticotroph adenoma was confirmed using the 10% criterion in 19 patients with Cushing’s disease and correctly identified 2 patients with ectopic disease. A pituitary corticotroph adenoma was confirmed using the 10% criterion in 19 patients with Cushing’s disease and correctly identified 2 patients with ectopic disease.

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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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 χ² criterion. The odds ratio was calculated using 2×2 table method. 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 (37.3%) 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 transsphenoidal surgery.

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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 bioavailability, 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, 15% 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 axis in patients with clozapine has not been reported. We present a case of a patient with clozapine use, and review the literature.

Case
A 38-year old male with clozapine treatment was referred for chronic symptoms of reduced libido and associated low testosterone levels. He was treated for clozapine in combination with testosterone replacement. Four months later, testosterone levels were confirmed low at 20 ng/dl with low gonadotropins (FSH 1.31 mIU/mL, LH 0.73 mIU/mL), normal prolactin 7.93 ng/mL, TSH 2.52 mIU/mL and T4 0.68 ng/dl (normal 0.84–1.76). IGF-I and morning cortisol levels were frankly low, at 26 mg/dl (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 x 10.7 mm. He was treated with 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 IGF-I, 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 (ICVdD); 76.0%) and 3) arthopathy (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%). CVdD's component conditions included hypertension (59.3%), myocardial hypertrophy (50.0%) and other various CVdD'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, most by 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 IGGSS. Pasireotide-LAR is a new multireceptor-targeted somatostatin receptor ligand that has superior efficacy over octreotide LAR to control GH and IGF-I levels. Little data is available about the efficacy and safety of pasireotide monotherapy in patients treated with a combination therapy.

Material and methods
Fourteen acromegalic patients (10 women, aged: 47.1±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
IGF-I 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 IGF-I 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-I (N=2), intolerance despite control (dizziness N=1 and hypoglycemia 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 IGF-I (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 IGGSS.

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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-I (IGF-I). While some studies have investigated the potential associations between biochemical control (i.e., normalization of IGF-I and/or GH) and comorbidities/symptoms, few studies have investigated 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, ≥ 2 valid readings of GH and IGF-I, and ≥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 ≤ the upper limit of normal, or GH measurements ≥ 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% 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 3.3 ± 11.9 μg/L and 367.7 ± 154.2 μg/L 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) and arthropathy (48.5%). 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.

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-I [IGF-I]) 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 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, ≥ 2 readings of GH and IGF1, and ≥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 ≤ upper limit of normal, or GH measurements ≤ 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 ≥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] 30.9%; 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: 98.6%). Results show that IGF1 and GH levels were initially elevated in the majority of patients, and declined over time. Biochemical control was reached by ≥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.

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 ≥ 30 kg/m2, 55 patients, control group < 30 kg/m2, 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 images (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).

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±11.09 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±1.45 ± 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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P877

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 CSOM230C20304 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±9.8; mean IGF-I: 3.58±1.2; 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) immunohistochemical expression of type V SSTR 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 17.36 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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P875

The change in metabolic parameters 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 150.3±29.3 to 121.7±18.5, p=0.30) decreased nonsignificantly accompanying a significant decrease in PRL levels (from 108.6±26.3 to 13.0±13.0, p<0.000) following therapy. The data were shown in detail in Table 1.

Conclusion
Metabolic variables such as FPG, LDL, 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>
<thead>
<tr>
<th>Table 1</th>
<th>The characteristics of prolactinoma patients before and after the treatment.</th>
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<tr>
<td></td>
<td>Time of diagnosis</td>
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<tr>
<td>PRL (mcg/l)</td>
<td>108.6 ± 13.1</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>94.4 ± 22.6</td>
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<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>115.3 ± 10.7</td>
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<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>51.6 ± 4.4</td>
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<tr>
<td>TG (mg/dl)</td>
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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 28.5 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-PSH, 4-ACTH, 1-PRL).

Results

Twenty-eight patients were submitted to conventional or fractioned stereotactic RT (mean daily dose 2.26 ± 1.1 Gy; mean dose 46.50 ± 9.2 Gy) and 5 patients were submitted to radiosurgery (mean dose 23 ± 6.2 Gy). Mean age on 1 st 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 = 13.1%), new visual deficit (n = 2.62%), hormonal deficit deterioration (n = 3.37%), de novo hormonal deficit (n = 14.58%), stroke (n = 2.62%), cognitive impairment (n = 6.18%) and death (n = 2). Medium time to development of 1 st pituitary deficit was 10 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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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-lateral(s)ellar 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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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). Acromegals with lower GLS had also statistically significant increase in parameters of LV thickness i.e. intraventricular 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/m², 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 Clínicas, 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 dizziness). 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 Endocrinology Department of a tertiary hospital between 2002 and 2017. Review of patients’ medical records and assessment 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 ophthalmoplegia (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 ophthalmoplegia/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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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 woman 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. Thryoid 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 640). 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 = 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, appropriately 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 Guidance 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 stt, 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 effective 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 naïve 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 ≥ 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±2550 ng/dl (from 228 to 12,420); 21 HTZ: 287±85 ng/dl (from 196 to 452); C: 305±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±23.1 ng/ml (from 3.5 to 51.5); 21 HTZ: 1.7±0.9 ng/ml (from 1.2 to 2.9); C: 1.4±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±0.32 ng/ml vs. 0.14±0.08 ng/ml in 21 HTZ and 0.11±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±46.9 ng/ml; corticosterone: 12.1±9.7 ng/ml) and C (cortisol: 169±26 ng/ml; corticosterone: 14.4±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 21-OHP, 17α-OH-progesterone, cortisol and corticosterone is a valid diagnostic tool in 21-NCAH patients.

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 2×10−6 M on viability 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 that 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.

Bone & Osteoporosis
P890
Bone mineral density in oligomenorrheic women with polycystic ovary syndrome
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Introduction
Oligomenorrhea have negative impact on bone mineral density (BMD). The aim of this study was to analyze BMD in oligomenorrheic 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±4.7 years, BMI: 24.9±6.1 kg/m²) and 22 healthy BMI-matched controls (HC) (age: 31.6±6.3 years, BMI: 24.9±6.1 kg/m²). In follicular phase of menstrual cycle we determined BMD by osteodensitometry, fasting serum glucose (FG), insulin, lipids, calcium, phosphate, albumin, PTH, testosterone, SHBG, DHEAS, 17OHP-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±0.8 vs. 1.4±0.5 mmol/l, P=0.05), androstenedione (3.2±1.1 vs. 1.9±0.4 ng/ml), corrected calcium (2.2±0.9 vs. 2.1±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 PTH (r=-0.65, P=0.022).

Conclusions
Oligomenorrheic women with PCOS did not differ in BMD to the BMI matched healthy controls.

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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 ± 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/m² 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 28.5±8.11 kg/m²; 19 patients had a BMI within target. Mean BP was 121.6±13.3/73.7±10.5 mmHg. Twelve patients were on anti-hypertensive agents (eight patients were on one agent treatment and four were taking two agents). Mean BP of those not on anti-hypertensive therapy was 117.3±12.2/72.2±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 HaA1c 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 HaA1c 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 had 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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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. Hysterecctomy at age 43 due to uterine fibroids. Physical examination: BMI 24.9 kg/m², 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: hematoctit 45.8%, TSH 2.7 μU/ml (0.35–3.7), FSH 64 μU/ml (> 30), LH 22 μU/ml (> 14), prolactin 5.5 ng/ml (< 25), estradiol 26 pg/ml (0–32.2), progesterone 0.7 ng/ml (< 1), 17-hydroxy-progresterone 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, abdominot 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 μU/ml, LH <0.07 μU/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/ml, FSH 57 μU/ml, LH 41 μU/ml

Conclusion

Despite its unusual cases 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

P894

Clinical Case Reports - Thyroid/Others

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 orchidectomy 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 × chromosomes from either parent. Its prevalence is 1 in 600. 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 has 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 (Swedlow 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 tumours confirmed the greatly elevated risk of lymphoma and breast cancer in 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.

DOI: 10.1530/endoabs.56.P894
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 162.5 cm, weight of 68 kg (BMI = 23.8 kg/m²), 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-microphallic-like appearance and hirsutism. No inguinal masses were palpable. The laboratory findings showed basal plasma cortisol: 19 μg/dl, ACTH: 49.96 μg/ml, androstenedione: 2.65 ng/ml, DHEA-S: 191.9 μg/dl, 17-OH Progesterone: 2.38 ng/ml, FSH: 91.45 μIU/ml, LH: 15.18 μIU/ml, estradiol: 16.45 pg/ml, testosterone: 234.5 pg/ml, dihydrotestosterone: 120 pg/ml, inhibin B: < 10 pg/ml, anti-Müllerian 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 sac, 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.

DOI: 10.1530/endoabs.56.P896
A 25 years old male patient with Noonan syndrome and delayed puberty

Evaluation of pubertal development in young with type 1 diabetes mellitus: about 200 patients

P901
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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 determine factors that influence pubertal development.

Evaluation of pubertal development in young with type 1 diabetes mellitus: about 200 patients
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Objective
To assess pubertal status in young patients with diabetes Type 1 and determine 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 department 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.

DO: 10.1530/endoabs.56.P901

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 HbA1c had only slight agreement (κ = 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 uncertainty 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 galactorhoea, 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 Dunnett’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 overweight) 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

DO: 10.1530/endoabs.56.P903
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 lines 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 (E2; 1 × 10⁻⁷ M), or fludioxonil (10⁻³ – 10⁻⁵ M). As results, in MTT assay for 9 days, E2 as a positive control markedly increased MCF-7 and T47D cell viability about 3.5 times and 2.2 times, and fludioxonil (10⁻³ M) also increased cell viability about 1.2 to 1.5 times compared to control. However, when fludioxonil 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-231 cells was not changed by treatment of fludioxonil and co-treated with ICI 182,780, as did E2. 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 and T47D cells by E2 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 E2 or fludioxonil was 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 confirm the molecular mechanism for support the change of cell viability and cell migration.

Key words: Breast cancer; estrogen receptor pathway; xenografted or orthotopic mouse models in which MCF-7 or T47D cells are injected or are injected into mammary fat pad.

DOI: 10.1530/endoabs.56.P904

Treatment of 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 (E2; 1 × 10⁻⁷ M), Fen (10⁻³ – 10⁻⁷ M), Cyp (10⁻³ – 10⁻⁷ M) in the absence or presence of ICI 182,780 (ER antagonist). As results, MTT assay, two-pesticides increased MCF-7 cell viability about two times compared to control like E2 (about 3.5 times). But, in the recent treatment of pesticide 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 E2 or two-pesticides compared to control. In colony formation assay, MCF-7 cells did form the colony by treatment of E2 and antifungal agents, but MDA-MB-231 cells did not form. However, E2 and antifungal agents, 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 E2 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 E2 or two-pesticides were maintained at the level of control. In migration assay, MCF-7 cells treated with E2 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.

Key words: Breast cancer; estrogen receptor pathway; xenografted or orthotopic mouse models in which MCF-7 cells are subcutaneously injected or are injected into mammary fat pad.

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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 exposures, such as bisphenol A (BPA). BPA is considered to play an important role in the etiopathogenesis 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 creatinine vs 1.65 ± 1.2 μg creatinine, P = 0.0035). BPA positively correlated with age (r = 0.01; R² = 0.1), SHBG (r = 0.05; R² = 0.07) and negatively with estrone (r = 0.005; R² = 0.12), DHEAS (r = 0.03; R² = 0.18) and free androgen index (FAI) (r = 0.05; R² = 0.08), respectively. Other steroid hormones (testosterone, free-testosterone, androstenedione, estradiol) and metabolic parameters (BMI, glucose, insulin, 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 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 mmol/l vs 65.63 ± 9.6 mmol/l; P = 0.046) as well as insulin (10.46 ± 1.8 μIU/l vs 15.2 ± 1.5 μIU/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 effect of bisphenols on steroidogenesis.

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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 2013 to 2017.
Primary endpoint was lipid profile change from baseline at 24 months. Secondary endpoints included change in body mass index (BMI), weight, blood pressure (BP) and glycaemic parameters. Statistical analysis was performed with SPSS Statistics 20.0.1. 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 ± 11.25 to 75.17 ± 19.04 (P=0.01) and from 23.84 ± 5.79 to 25.02 ± 5.85 kg/m² (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 (24.03 ± 4.04 to 25.32 ± 4.11 kg/m² (P=0.035)). No significant differences in lipid profile and blood pressure were observed in this group. Even though final values 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. 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 hermeneneutics 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 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 0.3–5.0 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 (US$) of prostate and 16/28 (57%) of our patients have had neither a PR nor an US$. 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 US$ 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 CXC4R4 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. CXC4R4 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 CXC4R4 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 estrogen receptor (ER), 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 CXC4R4 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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Background
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/ln(G) + ln(I); while IRI = 2×(INSp x GLYp) + 1, where INSp, GLYp = insulinaemic and glycemic areas during OGTT. McAuley index was calculated as Mffm/IZK

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<0.001). 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 above also 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 format. 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. 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 assess 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<0.05 was assumed. In the examined group the average BMI (kg/m²) was 28.0±6.9, BAI 32.7±6.4, VAI 17.5±8.8, WHR 0.8±0.1, WHR 0.8±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 (µU/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. LDL cholesterol was statistically lower in patients with higher BMI (P<0.05, r=0.40), BAI (P<0.05, r=0.3), VAI (P<0.05, r=0.54), WHR (P<0.05, r=0.25) and WHR (P<0.05, r=0.38). TGC correlated positively (P<0.05, r≥0.16) with BMI, BAI, VAI, WHR, WHR. There were not significant correlation observed among TC, LDL cholesterol and studied variables. Fasting glucose and insulin correlated positively (P<0.05, r≥0.23) with BMI, BAI, VAI, WHR and WHR. Women with higher value of HOMA-IR index had statistically higher BMI (P<0.05, r=0.45), BAI (P<0.05, r=0.27), VAI (P<0.05, r=0.46), WHR (P<0.05, r=0.46) and WHR (P<0.05, r=0.46). There was negative correlation (P<0.05, r>0.33) between anthropometric parameters and the value of QUICKI index. Positive correlation (P<0.05, r≥0.23) between CRP concentration and BMI, BAI, VAI, WHR and WHR 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 WHR 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>150mg/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, VAL, WHR, WHRR). To establish the statistical relationship statistically significant value P<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<0.05, r=0.35), as well as between VAI and predisposing CVD factors (P<0.05, r=0.26). WHR and predisposing CVD factors (P<0.05, r=0.38), also WHRR and predisposing CVD factors (P<0.05, r=0.39). Higher number of predisposing CVD factors connected to higher CRP concentration (P<0.05, r=0.22). The correlation between predisposing CVD factors and BMI (kg/m2) was observed (P<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 2850g with good perinatal outcome. During her postpartum hospitalization hypertensive peaks and a hypokalemia was observed and treated with valsartan 320 mg and Labetalol 400mg/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 eplerone, since the patient was already on spironolactone at time of consultation, was a female fetus and the lack of literature on eplerone 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 endocirdinal disorder affecting 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 Letrozole-induced 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 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 miscarriages.

Methods
Immunohistochemical endometrium study was performed on the immunostimulator Leica Bond-Max (Leica Microsystems, Germany). The expression value of markers IL-2 receptor, IL-1a, 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-1 beta (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 miscarriage 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 peripherally, 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±4.40kg/m²) 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 (mg/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 TSH (10.09±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) - TPOAb− 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 ERα, ERβ, 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 ERβ 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 no 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 vs. -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 (≈6.34 g/day) than in other groups however, other groups were found to be similar (≈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 (≈ 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 (≈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 (≈ 7 ng/ml, P < 0.05). 4-day estrus cycles of the control group were prolonged in food-restricted groups (≈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% (26/64) had menopause 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 dysgoblastoma) 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, citoromegaly, 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 after 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 fertile 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 Tac3 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 Per1, 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 TacR3/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. DOI: 10.1530/endoabs.56.P924

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 Cushings syndrome, Polycystic ovarian syndrome, benign and malignant androgen secreting ovarian tumors, ovarian hyperthecosis, adrenocortical tumours and iatrogenic hirsutism.

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. 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/ [<3.0 nmol/l], LH 42.4 mIU/ml, FSH 104.0 mIU/ml, DHEAS 0.9 mOL/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 mIU/ [0.35–5.5 mIU/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/agonists 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 development and differentiation. Evidence suggest their possible involvement in the pathogenesis of metabolic syndrome and probably in polycystic ovary syndrome (PCOS).

Aim
The 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 IGFBP3 levels.

Results
Nonobese PCOS women had higher IGF1 than those with BMI > 25 with borderline significance (211 ± 15.6 vs. 160.7 ± 16, P = 0.06). No significant differences in serum IGF2 and IGFBP3, levels in women according to BMI have been detected. IGF1 negatively correlated with HOMA IR (R² = 0.23, P = 0.03), waist circumference (R² = 0.15, P = 0.045) and triacylglycerols (R² = 0.23, P = 0.02), but not with sexual steroids. On the other side IGFBP3 was in positive correlation with TAG (R² = 0.22, P = 0.0215), total cholesterol (R² = 0.02, P = 0.028), LDL cholesterol (R² = 0.2, P = 0.03), dihydrotestosterone (R² = 0.14, P = 0.049) and estrogen (R² = 0.21, P = 0.014). Neither correlation between 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 immunosassays, 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), 17OHprogestosterone/progesterone (P < 0.001), 17OHprogestosterone/17OHpregnenolone (P = 0.004), androstenedione/dehydroepiandrosterone

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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 non-endocrine 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/m² 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. DOI: 10.1530/endobbs.56.P928

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 in 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/m². 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 detected 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 CSA (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, 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, 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 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 uU/ml (normal:2.6–24.9 uU/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 CSA 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 have 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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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, craniophar-rynigomas, 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 HIL, 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 uterine volume, correction of treatment 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) eFSH doses in case of low number of antral follicles, estrogen treatment continuation during ovarian stimulation, addition of rLH 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 polycystic ovary syndrome

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Hypertestosterone is a common finding in women with polycystic ovary syndrome (PCOS). As a result of the PCOS hyperandrogenism, various adverse metabolic outcomes have been observed, including insulin resistance, diabetes, hypertension, dyslipidemia, obesity, nonalcoholic fatty liver disease, and hypercoagulability. Women with PCOS also have an increased risk of cardiovascular disease (CVD). Obesity is a major risk factor for CVD and is linked to the inflammation-mediated pathogenesis of atherosclerosis. However, the association of central obesity and inflammation markers with PCOS has not been well described. In this study, we investigated the association of central obesity and four inflammatory markers (interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), high sensitivity C-reactive protein (hs-CRP), and fibrinogen) with PCOS status in a larger cohort of women. Methods: A total of 220 women 18–40 years of age were recruited. Serum levels of IL-6, TNF-α, hs-CRP, and fibrinogen were measured by ELISA. Results: In the present study, women with PCOS had significantly higher levels of IL-6, TNF-α, hs-CRP, and fibrinogen compared to non-PCOS women. Additionally, higher levels of IL-6 and TNF-α were observed in women with central obesity compared to women with normal weight. Conclusion: This study suggests that inflammation markers may be associated with PCOS and central obesity, which could be a potential target for improving metabolic outcomes in women with PCOS. Further research is needed to confirm these findings and investigate the potential mechanisms underlying the association between inflammation and PCOS.
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 inflammation 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 WHR levels. PCOS was diagnosed according to Rotterdam criteria. A WHR cutoff of 0.5 was used as an universal cutoff for central obesity in adults. Therefore 156 low-WHR and 88 high-WHR PCOS patients were included in the study. High-WHR 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-WHR PCOS patients. L/WCC was lower in high-WHR vs. low-WHR PCOS patients. There was positive correlation between PLT/MPV and CRP, cholesterol, LDL, HDL, 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 associated 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=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.

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). 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-g 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 ≥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 ≥ 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 ≥ 140 mg/dl after OGTT was observed in the 66% of the cases who previously had glucose values ≤ 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 consistence 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 dissatisfacted 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 [1.691–3.563] and 2.921[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 ovaries

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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 findings 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 min after training, whatever the TOD, Lac, CK or LDH increased significantly (P < 0.01), whereas, no significant TOD effect on Lac, CK or LDH was observed. 3 min 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 ratio were registered only after morning training. 3 min and even 48 h 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. 3 min 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

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 MRKHS 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 orifice. 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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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 mIU/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.

P946
Primary amenorrhea due to gonadal dysgenesis in a girl with karyotype 46,XX
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Introduction
Gonadal dysgenesis is a rare case of primary amenorrhea, 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, E2= 5 pg/mL), subclinical hypothryoisim (TSH =5.1 mU/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 beginning 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 amenorrhea. 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 two abnormally functioning women with PCOS
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Introduction
Hyperandrogenism (HA) is frequent but not universal characteristic in women with polycystic ovary syndrome (PCOS). According to the ESHRE/ASRM definition, hyperandrogenism criterion could be clinical (hirsutism) and/or biochemical (hyperandrogenemia). 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±2.5 kg/m2), 2) with biochemical HA only (PCOS-BHA:N=151, age: 25.5±5.3 years, BMI: 24.5±6.5 kg/m2), 3) with both clinical and biochemical HA (PCOS-CBH:A:N=240, age: 25.0±5.2 years, BMI: 26.4±6.2 kg/m2), and 104 healthy controls (age:29.2±5.8 years, BMI: 25.4±16.8 kg/m2). CHA was defined as Ferriman-Gallwey score ≥ 8, BHA as presence of FAI≥2% and/or testosterone >2 nmol. We measured fasting glucose (FG), insulin, lipids, FSH, LH, testosterone, SHBG, androstenedione, estradiol, DHEAS and 170HProgesterone, while HOMA-IR and FAI were calculated. Differences between-groups were age and BMI adjusted.
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-BHA had higher 17Oprogesterone ([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 17Oprogesterone ([P=0.030] and [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/L, LH level of 41 mIU/mL and a estradiol level <9 pg/mL. Pelvic ultrasonography showed a hypoplastic Uterus without visualization of the ovaries. Cyto genetic 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 46,X,r(X) metaphase. Laboratory investigations revealed normal hematological and biochemical parameters except for Alanine amino transferase (ALT) ([87]UI/L>45UI/l) and Alkaline phosphatase (AP) ([819]UI/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 not 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 (220UI/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-progesterin 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/m²), and 82 BMI-matched healthy controls (age 29.2±5.9 years, BMI 23.3±8.6 kg/m²). In follicular phase of menstrual cycle we determined fasting serum fasting glucose (FG), insulin, lipids, CRP, testosterone, SHBG, DHEAS, 17O-progesterone, androstenedion, estradiol, TSH, fT4, CIMT and blood pressure (BP). HOMA and FAI were calculated. Differences 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<0.001]), testosterone ([P<0.001]), DHEAS ([P<0.001]), androstenedione ([P=0.002]), 17Oprogesterone ([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 CMT, 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 CIMT 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 (NOs) 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/m², [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-androstenedione ($P=0.008$) levels, while SOD activity was positively correlated with total testosterone ($P<0.001$), D4-androstenedione ($P=0.001$), DHEAS ($P=0.023$) 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 counterbalance 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 study 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-HT, $N=27$; age: $25.8\pm 5.2$ years, BMI: $28.5\pm 7.3$ kg/m$^2$) and without HT (PCOS-HT, $N=140$, age: $25.1\pm 2.4$ years, BMI: $24.5\pm 5.9$ kg/m$^2$) and also 48 healthy controls (HC) divided on HT (HC-HT, $N=10$, age: $25.8\pm 5.2$ years, BMI: $23.1\pm 3.8$ kg/m$^2$) and without HT (HC-HT, $N=38$, age: $29.7\pm 6.3$ years, BMI: $23.6\pm 6.2$ kg/m$^2$). In follicular phase of menstrual cycle we determined fasting serum glucose (FG), insulin, lipids, CRP, testosterone, SHBG, DHEAS, 17OHP-gestosterone, androstenedione, estradiol, TSH, FT4, FT3. HOMA and FAI were calculated. Differences between groups were age-adjusted.

**Results**

PCOS-HT had highest BMI than all other groups ($28.7\pm 1.2$ kg/m$^2$) and significantly differed from all other groups; vs. PCOS-HT ($24.7\pm 0.5$ kg/m$^2$), $P=0.02$; vs. HC-HT ($23.1\pm 3.8$ kg/m$^2$), $P=0.02$; vs. HC-HT ($23.7\pm 6.2$ kg/m$^2$). There was no difference in any other measured parameter between PCOS-HT and PCOS-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 8,659 clinic visits from 829 women with TS and liver enzymes; ALT, AIKP and 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, AIKP 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 $P<0.05$).

**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 AIKP. 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 pregnancy 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 fertility 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 guidelines 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 (IVT, 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 thrombophilia 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 a miscarriage but had a miscarriage, 4 had not got pregnant (6.6%). In 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 lower 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 alpha-hydroxylase deficiency is a rare form of congenital adrenal hyperplasia. It is characterized by amenorrhea, impuberism, hypertension and hypokalemia. We report a case of 17a-hydroxylase deficiency in a patient with a 46,XX karyotype, which contrasted with the absence of Mullerian duct.  

Case report  
An 18-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 (SP1 stage of Tanner classification) and normal female pre-pubertal external genitalia. The karyotype was 46, XX. Biological examination showed hypokalemia, primary hyperaldosteronism and low levels of all steroid hormones requiring alpha-hydroxylation (cortisol, 17a-hydroxy progesterone, dehydroepiandrosterone sulfate, 11-desoxycorticisol, Δ4 androstenedione and testosterone). Thus, the diagnosis of 17alpha-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 kalemia. 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 alpha-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 duct in 46,XX subjects with 17 alpha-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, triglycerides, 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 OGT 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 OGT. Patients with developed GDM were older(28.73 ± 2.01 vs25.22 ± 1.78 years), with higher BMI(28.57 ± 4.02 vs26.46 ± 1.26 kg/m2), with higher levels of triglycerides (2.26 ± 0.87 vs1.87 ± 1.12 mmol/l), higher levels of hsCRP(2.32 ± 0.99 vs1.76 ± 0.76) and lower levels of HDL (1.20 ± 0.16 vs1.41 ± 0.32 mmol/l) (P<0.05). The levels of cholesterol (4.24 ± 1.24 vs4.27 ± 0.85 mmol/l) and LDLc (2.87 ± 0.56 vs3.29 ± 0.71 mmol/l) were similar (P>0.05). Seven(58.33%) of GDM patients have DM in family. Fifteen(14.7%) of nonGDM 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.
Material 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 electrochemiluminescence 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 (9.4%) and gynecology (8.2%) departements. Mean value of Testosterone and prolactin were 4,42±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 OHP 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, autosomal 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. Ultrasoundography demonstrated 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 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, gynaecomastia, 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 hypoplasias, 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 gynecologist because of a history of several years of infertility and established azoosperma. 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 azoosperma or severe oligosperma. 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 were elevated, normal sex steroid levels and no choriocarcinoma. Leydig cell hyperplasia was present without Leydig cell 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 measured 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 IU/L, FSH 10.3 IU/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 gonadotrophins. Sperm production can be restored in cases with high intratesticular testosterone receptors.

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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) – WNNIN/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
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. 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 = 0.20, P = 0.013), and PLR. (r = −0.02, P = 0.14).

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 naive young patients with CHH did not have any effect on the platelet count and size.

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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 unsellected 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 = 1.1–4.4); 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 ± 6.9 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 cyionate every 21 days, starting the treatment with 250 mg of i.m. testosterone cyionate every 21 days, testosterone between 2016 and 2017. Average was 23.9 ± 6.9 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 cyionate every 21 days, starting the treatment with 250 mg of i.m. testosterone cyionate every 21 days, testosterone between 2016 and 2017. Average was 23.9 ± 6.9 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 cyionate every 21 days, starting the treatment with 250 mg of i.m. testosterone cyionate every 21 days.

Results
There was a mean increase in weight after 3–4 months of treatment (72.4 ± 23.4 kg vs 74 ± 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 ± 2.1 kg). Testosterone treatment was associated with an increase in LDL levels, from 99.4 ± 32.7 mg/dl to 105.4 ± 32.2 mg/dl (P = 0.017) and TG levels, from 69.8 ± 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 ± 2.25 vs 12.1 ± 7.9 µmol/l, P = 0.037). Fasting glucose level dropped from 9.6 ± 2.5 vs 41.02 vs 38.2 mg/dl (P = 0.048). Fasting glucose level dropped from 9.6 ± 2.5 vs 124.7 ± 39.9 mg/dl (P < 0.001) and hemocytot (40.7 ± 3.0 vs 44.2 ± 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 hypogonadotropic 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 ± 4.15 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) 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 transsexual men and in the first 3–12 months in transsexual females.

Objective
To examine the effects of cross-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 ± 12.15 years, mean duration of CHT of 24.7 ± 39.9 months. In MTF(68.8% oral estradiol, 31.2% estradiol transdermal patch,33.3% 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 ± 8.43(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). FMI (76.9% testosterone cyionate,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) from 41.92 ± 6.75 to 40.60 ± 6.75 (P = 0.04).

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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 neurovascular 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 lifestyle. 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 ED) and 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 ever been 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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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 testsis 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 our 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 testsis 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 testsis, while in the epididymis leptin increases spermatozoa differentiation. However, it is still 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 hypogonadotropic hypogonadism.

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unclear why leptin would accumulate in the seminal vesicles. Leptin and the soluble leptin receptor (LeptRe) have been recovered from ejaculate and, leptin is known to facilitate in vitro fertilisation and implantation, and LeptRe increases the half-life of leptin. Thus, leptin in the male reproductive tract may play a role in the normal fertilisation and implantation processes.

Objective

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 study, 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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**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±11.63 years). 68.8% with oral estradiol mean doses 17.18±5.74 mg/week, 31.2% estradiol transdermal patch mean doses 45.15±36.85 mg/week and 78.3% plus cyproterone acetate mean doses 52.13±22.99 mg/day. Prior to treatment, prolactin levels (PRL) were 13.97±9.33 ng/mL; estradiol (E2) 43.90±30.27 pg/mL; testosterone (T) 274.88±215.41 ng/dL; LH 4.78±5.51 mIU/mL and PSH 5.16±6.44 mIU/mL. After a mean follow up of 24.7±35.6 months, PRL increased to 23.54±14.19 ng/mL (P<0.02), E2 to 48.89±24.92 pg/mL (P<0.03), T2 dropped to 112.25±160.03 ng/dL (P<0.023), LH to 2.01±3.42 mIU/mL (P=0.021) and FSH to 2.60±4.34 mIU/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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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 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 is associated with decreased thyroid hormone levels during the uterine life in boys born with such semen quality and higher risk of testis cancer. Several factors seem implicated in the pathogenesis of this congenital abnormality.

Methods

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 T3, 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: ≥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.

References

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Proteins, simultaneously activating Ca\(^{2+}\) and cAMP.

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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**

**In vitro characterization and comparison of commercial GnRH antagonists**

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**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 GnRH-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 overexpressing GnRHR (cAMP EC\(_{50}\) = 11.58±0.29 nM, n = 3; Ca\(^{2+}\) EC\(_{50}\) = 25.97±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 Ca\(^{2+}\) accumulation in SH-SY5Y cells expressing endogenous GnRHR (P < 0.05, one-way ANOVA; n = 3). In GnRH-transfected HEK293 cells, Ca\(^{2+}\) increase induced by treatment using concentration of 3-fold the EC\(_{50}\) of GnRHR 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-μM 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 not be equivalent in vitro, drug-specific effects in vivo should not to be excluded.

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**Steroid metabolism + action**

**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 gomion landmark shifted towards 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 (CST) 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 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 administration.

**Results**

Of the 1218 patients included, 24.8% developed a hematocrit (Ht) >50%, 4.2% had a maximum hematocrit of >50% 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 >50%. 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 to 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-BHSD3 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**

Case 1: A 2-year-old girl presented with ambiguity of external genitalia. 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 stage1). Pelvic ultrasound and MRI showed inguinal and rose to 3 ng/ml after HCG stimulation. The serum androstenedione (A) was high 0.8). The karyotype was XY. The serum testosterone was 2.82ng/ml. The serum androstenedione was high at 7 ng/ml (three times the upper limit of normal). The T:A ratio was 0.3 (<0.8) after HCG stimulation. Diagnosis of 17-BHSD3 deficiency was confirmed with genetic mutation of the 17-BHSD3 gene.

**Conclusion**

We have described 3 patients with classic clinical and biochemical features of 17-BHSD3 deficiency in whom a mutation was identified in the 17-BHSD3 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 orchiectomy 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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**P984**

**Thyroid (non-cancer)**

**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.

DOI: 10.1530/endoabs.56.P984
Poster Presentations: Thyroid
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 μU/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 propylthiouracil was withdrawn 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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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 hyperthyroid 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 compliance. 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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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 illness. 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 examinations and treatment.

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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 dysfunction through different mechanisms, 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 μIU/ml (normal range 0.5–4.5 μIU/ml), a mean 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 μIU/ml and an improvement in renal function from a 1.63 mg/dl creatinine level to 0.85 mg/dl. Also, the patient 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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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 report 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, 6.9x8.6 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/mm³), elevated CRP (23.7 mg/dl), creatinine (1.5 mg/dl) and PTH (698 pg/ml); normal free T4 (1.2 ng/dl) and thyroglobulin (32 ng/ml) levels. Ultrasonography revealed hypoechoic nodular thyroid gland and a 7.5x7.0 cm heterogeneous cyst. Neck computed tomography showed a 7.5x7.0 cm diameter abscess on the right cervical region extending to the upper mediastium. Thyroid and parathyroid scintigraphies (Tc-99m pertechnetate 4+ Tc-99m MIBI) revealed that the mass was unrelated to these glands. Secondary hyperparathyroidism due to vitamin D deficiency was diagnosed. Empirically mesoprenon and teicoplanin were administered. The drainage of the abscess was performed with micro puncture. Because of the mediastinitis risk, the abscess was drained totally. Mycobacterium tuberculosis was detected with polymerase chain reaction of suppurrative 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 patients, it may appear late 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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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 hypofunctional, 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)).
Introduction

De Quervain’s Thyroiditis (DQT) is a self-limiting 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 l (3.54-5.14), anti-TSH-R 3.9 U/l (n<9), anti-TPO 7 U/l (0-12), anti-Tg 316 U/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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### P995

Coexistence of Hashimoto thyroiditis and De Quervain’s thyroiditis

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Introduction

Coexistence of hashimoto thyroiditis and De Quervain’s thyroiditis (2) abnormalities. The chest radiography showed severe cardiomegaly. An edema. GFR examed revealed blood pressure of 120/60 mmHg, pericardial rub, and no biochemically euthyroid on Methimazol 20 mg daily 1 year before. The hyperthyroidism was diagnosed 1 year before; she was clinically and A 25-yr-old woman was admitted with a recent history of dyspnea. A Graves’ developed a syndrome of pericarditis as the first sign of ANCA associated vasculitis 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 developed necrotic-looking vasculitic skin lesions on bilateral lower extremity and on her right ear. Skin biopsy showed leukocytoclastic vasculitis. The methimazol induced vasculitis 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 vasculitis.

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### P996

Tea and juice as a causes of levothyroxine malabsorption and intermittent hypothyroidism: a case report

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Introduction

Biological causes 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. Basedow and in october 2011 near thyroidectomy was done. In 2012 desparte 200 mg LT4 her TSH had been always elevated. She was admitted to hospital in december 2017 with levothyroxine dosage of 700 mg. In the last few months she was treated with Novothyral preparation 100, 3 tablets per day (combination of levothyroxyn 100 mg and liothyronin 20 mg) but without success. During 6 years period patient did have 24 controls (four per year) by secondary term 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 mg. During all these years transient hypothyroidism has been presented. Values of hormones were as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>SD</th>
<th>Median</th>
<th>MIN-MAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH mIU/L</td>
<td>&gt; 100</td>
<td>9.4</td>
<td>55.7</td>
<td>61.94</td>
</tr>
<tr>
<td>FT4 pmol/L</td>
<td>5.9</td>
<td>10.8</td>
<td>12.8</td>
<td>7.8</td>
</tr>
<tr>
<td>FT3 pmol/L</td>
<td>7.4</td>
<td>18.2</td>
<td>18.3</td>
<td>2.5</td>
</tr>
</tbody>
</table>

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was scheduled for follow-up. Approval. No further treatment was deemed necessary at this time and the patient started using the drug with water. Her latest dosage of levothyroxine is 100 mg and current control of hormones in referred range.

Discussion

LAT in our testing excluded malabsorption 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.

After the test we obtained the data that she was taking levothyroxine on empty stomach 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 mg and latest control of hormones in referred range.

Discussion

LAT in our testing excluded malabsorption 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.

**Table: Levothyroxine Absorption Test (LAT) with 1000mg levothyroxine**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>0.h</th>
<th>1.h</th>
<th>2.h</th>
<th>3.h</th>
<th>4.h</th>
<th>5.h</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH mIU/L</td>
<td>4.16</td>
<td>3.77</td>
<td>3.52</td>
<td>3.36</td>
<td>2.65</td>
<td>3.06</td>
<td>0.35-4.94</td>
</tr>
<tr>
<td>FT4 pmol/L</td>
<td>12.1</td>
<td>16.86</td>
<td>23.91</td>
<td>24.26</td>
<td>26.76</td>
<td>22.48</td>
<td>9-19</td>
</tr>
<tr>
<td>FT3 pmol/L</td>
<td>7.4</td>
<td>7.35</td>
<td>7.67</td>
<td>7.43</td>
<td>7.6</td>
<td>6.97</td>
<td>2.6-5.7</td>
</tr>
</tbody>
</table>

**P997**

**Thyroid-type malignancies in struma ovarii and thyroid gland of two different origins**

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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 consists 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 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 the 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 the minor risk for recurrence. Adrenal adenoma was evaluated by the incidentaloma algorithm and no hormonal activity was detected. In her medical history, she had acute neurinoma operation and postoperatively uses small doses of bromocriptine because of hyperprolactinemia. Genetic analysis was performed but neurofibromatosis type 2 diagnosis and other genetic 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 multinodular goiter that occupied the entire anterior cervical area. On 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 thyrotoxic 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 pseudothyroparathyroidism, excluded by genetic tests (karyotype 45, XX), normal phospho-calcic profile but without the possibility for GNAS1 testing. Subsequent investigations revealed an elevated TSH (7.1 μIU/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 unsuppressed with high fT4. Five years later, after therapy had been discontinued for 3 months, she was admitted for reevaluation: tachycardia (100/min), persistent high TSH (7.88 μIU/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 which raised the suspicion of a TSHoma or an incidental macroadenoma. Sex-hormone binding globulin, ferritin and thyroglobulin were normal and the ultrasonography showed no goiter. On the TRH stimulation test, the brisk response of TSH (from 6.59 μIU/ml at 20 min) was suggestive for RTH. In January 2018, the patient underwent transsphenoidal pituitary adenectomy and after removal of the tumour TSH value suddenly decreased to 0.2 μIU/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 ferritin, 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 ruling out other possibilities of hepatic pathology, especially autoimmune disease. We report the case of a 6-year-old girl with Graves’ disease who presented a liver dysfunction.

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 bilirubiniaemia at 48 mmol/L. Abdominal ultrasound revealed hepatomegaly with a hetero-micronodular appearance. Cholangitis-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
Hepatic manifestations of hyperthyroism 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 hepatic.

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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 dysmorphism, 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 dysmorphism 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 U/l > 45 u/l), ALT (87 U/l > 45 u/l) and ALP (819 u/l > 200 u/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 Turner’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 tract 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 concomitant viral meningitis and acute Epstein-Barr virus infection. She presented with severe 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, prebital edema, pansystolic murmur in the left parasternal 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 T4>4.03 ng/dl (N 0.90-1.80), T3>9.94 pg/ml (N1.80-4.20) and normocytic anaemia. Electrocardiogram showed bradycardic (40/min) sinus rhythm. 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, T4 and T3 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 crisis 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
Adductive drugs like prednisolone and potassium iodide play an important role in preparing patients with resistant thyrotoxicosis 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 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
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 \( [\text{TSH}=1.07 \, \mu\text{U/mL}; \text{FT4}=1.11 \, \text{ng/dL}] \). Nine months after delivery she repeated laboratorial evaluation \( [\text{TSH}=16.3 \, \mu\text{U/mL}; \text{FT4}=1.04 \, \text{ng/dL}] \) and her general practitioner increased levothyroxine dose to 137 mcg. However, two months later her TSH was still high \( [\text{TSH}=14.62 \, \mu\text{U/mL}; \text{FT4}=0.91 \, \text{ng/dL}] \) 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 vertigo syndrome). On that occasion, she disclaimed intermittent compliance with levothyroxine therapy. Her laboratorial re-evaluation revealed a TSH of 159.43 \( \mu\text{U/mL} \) and FT4 of 1.04 ng/dL. She was summoned to repeat analysis and advised to withhold levothyroxine. She denied exposure to other medications, St.John’s work, 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: \( \text{TSH}=31.86 \, \mu\text{U/mL}; \text{FT4}=1.38 \, \text{ng/dL} \). The laboratory was requested to exclude macro-thyrotropin: serial dilutions revealed a linear recovery. The sample was also analysed by a different method/laboratory: \( \text{TSH}=38.46 \, \mu\text{U/mL}; \text{FT4}=1.45 \, \text{ng/dL} \); 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 \( \mu\text{U/mL} \) 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 intercurrent 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 HI 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 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 mg/mL. There was statistically significant difference of all the pro-inflammatory cytokines compared to controls \( (P \text{ value} < 0.05) \).

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, Goser, Autoimmunity, Leptin

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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. Sample serum 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.

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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, Goser, Autoimmunity, Leptin

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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 thyrometabolites of thyroxine (T4) also play an important physiological role. For example, 3,5-diiodo-L-thyronine (T2) and 3,3′-diiodo-L-thyronine (rT2) can suppress the thyroid stimulating hormone (TSH) level and increase the resting metabolic rate. 3-iodothyronamine (T1AM) administration in mice leads to a suppress the thyroid stimulating hormone (TSH) level and increase the resting metabolic rate. 3-iodothyronamine (T1AM) administration in mice leads to a

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Endocrine Tumours and Neoplasia

P1009

Bispectral System for Reporting Thyroid Cytology (BSRTC): Category III and IV Frequency and Risk of Malignancy in 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 cytology 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 FAs 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 clinic 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, node size, and a cumulative score of 5 suspicious sonographic characteristics were not predictive of malignancy in either category.

Conclusion

The utilization 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 recently 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 immunonephelometry.

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 ± 26.9 pg/ml (range:1.02–756). 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 405.71 ± 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; logically, 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;
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-glucuronate 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.

DOI: 10.1530/endoabs.56.P1010

Nuclear Receptors and Signal Transduction

P1011

Are benign adenoma and papillary thyroid carcinoma related? A linkage study from BRF and NIS gene mutation point of view

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Introduction

The adenoma – carcinoma sequence in thyroid nodules is an 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 to 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. Tumor 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

Our data showed high frequency of subclinical hypothyroidism in girls with TS. Thyroid autonomy 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 radiiodine 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 radioactive iodine (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 Graves’ disease, 32% had toxic multinodular goiter and 3% had toxic single nodule. Sixty-five percent had Graves’ disease, 32% had toxic multinodular goiter and 3% had toxic single nodule. Sixty-five percent had Graves’ disease, 32% had toxic multinodular goiter and 3% had toxic single nodule.

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±3.4 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).

Conclusions

Our data showed high frequency of subclinical hypothyroidism in girls with TS. Thyroid autonomy in TS patients is more often detected in the presence of structural anomalies of the X chromosome.

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Endocrine Abstracts (2018) Vol 56
**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 levels 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 Governate, Kurdistan Region, Iraq 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 CV 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’ ophthalmopathy**
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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, nasal 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/m². 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 mU/l) 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 (15 mg) and propranolol (20 mg×3) was then initiated. Lubricating eye drops were prescribed for the ocular symptoms. Thyroid hormone levels normalized (15 mg) and propranolol (20 mg×3) was then initiated. Lubricating eye drops were prescribed for the ocular symptoms. Thyroid hormone levels normalized (15 mg) and propranolol (20 mg×3) was then initiated. Lubricating eye drops were prescribed for the ocular symptoms. Thyroid hormone levels normalized.

**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 euthyroidism 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 quantitative 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 thicknesses 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.**

<table>
<thead>
<tr>
<th>Study group</th>
<th>Control group</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=50</td>
<td>n=50</td>
<td></td>
</tr>
<tr>
<td>Subfoveal</td>
<td>304.22±36.09</td>
<td>275.84±34.20</td>
</tr>
<tr>
<td>Temporal, 500 μm</td>
<td>311.06±38.18</td>
<td>274.22±34.92</td>
</tr>
<tr>
<td>Temporal, 1000 μm</td>
<td>309.68±36.83</td>
<td>272.98±33.24</td>
</tr>
<tr>
<td>Temporal, 1500 μm</td>
<td>302.00±32.44</td>
<td>267.64±31.77</td>
</tr>
<tr>
<td>Nasal, 500 μm</td>
<td>294.10±34.74</td>
<td>270.79±34.66</td>
</tr>
<tr>
<td>Nasal, 1000 μm</td>
<td>274.50±38.92</td>
<td>263.50±34.06</td>
</tr>
<tr>
<td>Nasal, 1500 μm</td>
<td>256.4±43.27</td>
<td>253.10±34.73</td>
</tr>
<tr>
<td>Mean</td>
<td>293.08±34.81</td>
<td>268.9±33.11</td>
</tr>
</tbody>
</table>

*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.

DOI: 10.1530/endoab.s.56.P1016

**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).

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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 thyroideectomy 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 disease were included. Five forms of thyroid disorders have been identified: Isolated hypothyroxinemia, Overt Hypothyroidism, Subclinical Hypothyroidism, Overt hyperthyroidism and Subclinical hyperthyroidism. Clinical and biochemical 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 33% 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.

DOI: 10.1530/endoabs.56.P1018

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 goiter (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 goiter (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 goiter, 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 goiter, and 22% (n=4) had toxic nodule. 50% (n=61) patients developed permanent hypothyroidism within 6 months of radioiodide 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 thyroideectomy, 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.

DOI: 10.1530/endoabs.56.P1019

P1020
How evolve antithyroperoxydase antibody in Hashimoto thyroiditis in time: Study on 450 patients
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Aim
Most research teams analyze the evolution of patients with Hashimoto thyroiditis (HT) on syndromal basis, not on pathogenic 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 accredited Bucharest laboratories. (2) Only patients with minimum 3 investigations were considered for interpretation. (3) We considered 5 ATPO evolutive patterns: (a) undulatory; (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 u/ml).

Results
(A) Patients: 450; women – 421, men – 29 (6.89%). (B) The reinitialization 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 u/ml, standard deviation: 2508. (D) The evolution patterns were: (a) undulatory – 313 patients (69.5%); 5 without thyroid; (b) decreasing (ATPO over cut off limit) – 76 (17%); 3 no thyroid (1 – atrophy, 2 thyroideectomy/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) undulatoryious: 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: Hyperthyroidism vs euthyroidism vs hyperthyroidism: (a): 153-113-47; (b): 31-30-15; (c): 16-13-7; (d): 3-7-2; (e) test, Z=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.

DOI: 10.1530/endoabs.56.P1020

Endocrine Abstracts (2018) Vol 56
P1021
Hyperemesis gravidarum mimicking thyroid storm- A diagnostic dilemma in early pregnancy
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Introduction
The thyrotrophic effects of human chorionic gonadotropin (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.

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.

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 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.

Results
The mean age of study group was 50 (range interval = 14–90) years. The median of node-diameter 1 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, 28.3% benign, 0.4% suspicious for follicular nodule, and 1.2% malignant.

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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Department of Endocrinology and Metabolism, Kartal Dr. Lutfi Kirdar Research and Training Hospital, Istanbul, Turkey.

Background/aim
We aimed to determine the effect of percutaneous ethanol injection (PEI) on volume of cystic and mixed thyroid nodules, thyroid function tests (TFTs), antibody titers and cytologic 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, 6th and 12th months. Fine needle aspiration biopsy (FNAB) was performed to PEI applied nodules in the 12th month. Thyroid nodules were grouped into three by structural properties (pure cystic, predominant cystic, predominant solid).

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 autoantibodies, 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.

Conclusion
The correlation between cytologic results and thyroid autoantibodies, calcitonin, and thyroid function tests (TFTs), antibody titers and cytologic changes for 1 year.

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P1022
Correlation between cytologic results and thyroid autoantibodies, calcitonin, and thyroid function tests in patients with thyroid nodules

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 titters (4.37 ± 2.95 U/l versus 7.25 ± 7.22 U/l NS) and MMI starting dose (20.3 ± 8.0 mg/day versus 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 group (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-hydroxvitamin 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 follow-up for 18 years for MNG. She developed hyperthyroidism (FT4 = 35 mU/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 osteoporosis. 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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P1026

The thyrotoxicosis in patients with amiodarone induced thyrotoxicosis may not respond toperative 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 Type2 diabetes and ventricular arrhythmia which were treated with intensive insulin therapy and 200 mg amiodarone/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, propranolol 80 mg/day, methimizole 40 mg/day and methylprednisolone 60 mg/day were started. However, FT4 levels increased to >7.7 ng/dl 3 weeks after treatment. Therefore, thyroidecotomy 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 thyroidecotomy was performed without any complication.

Case 2
A 74-year-old male patient with acute anterior myocardial infarction (AMI) induced by Graves’ disease was admitted to emergency department and underwent coronary angiography 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 could not be achieved 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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P1027

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-stimulating hormone (TSH). Owing to Paucity of studies regarding the effect of metformin on TSH in hypothyroid patients, this study compares the effect of metformin on TSH and BMI in Egyptian naive 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 (28.8 ± 2.2, 97.2 ± 6.7) and (28.8 ± 1.8, 104.8 ± 5.4, P < 0.001) 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 naive hypothyroid Egyptian patients with no influence on TSH levels.

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P1028
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 Bioscences). 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 TgAbs were detected with biotin-conjugated anti human IgG or IgM HRPO- conjugated streptavidin 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 1/300 (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 radiofrequency ablation: results at 6 months in 17 patients
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Introduction
Radiofrequency ablation (RFA) represents an alternative to surgery for benign thyroid nodules with pressure symptoms or evident progressive growth.

Objectives
To analyze in our center the efficacy and safety at 6 months of a single treatment of RFA performed in predominantly solid thyroid nodules.

Methods
One single session treatment of RFA is an effective and safe outpatient procedure for 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 proportion 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±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.

<table>
<thead>
<tr>
<th></th>
<th>Euthyroid GD</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>64</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.6±10.9</td>
<td>48.0±10.8</td>
<td>0.8523</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>51:13</td>
<td>50:14</td>
<td>0.828</td>
</tr>
<tr>
<td>Corrected calcium (mg/dI)</td>
<td>9.12±0.48</td>
<td>9.23±0.29</td>
<td>0.1874</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>4.24±0.78</td>
<td>3.84±0.51</td>
<td>0.0044</td>
</tr>
<tr>
<td>25OH-Vitamin D (ng/ml)</td>
<td>16.40±5.52</td>
<td>23.20±5.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>15.29±8.82</td>
<td>25.79±11.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FGF23 (ng/ml)</td>
<td>59.10 (45.18-96.09)</td>
<td>46.00 (27.21-60.55)</td>
<td>0.0003</td>
</tr>
<tr>
<td>PINP (nm/l)*</td>
<td>49.70±19.65</td>
<td>54.12±20.65</td>
<td>0.5293</td>
</tr>
<tr>
<td>CTX (ng/ml)*</td>
<td>0.21±0.12</td>
<td>0.23±0.09</td>
<td>0.5995</td>
</tr>
</tbody>
</table>

*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.

<table>
<thead>
<tr>
<th></th>
<th>Euthyroid Graves’ disease group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>Regression coefficient</td>
<td>−31.6</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.015</td>
</tr>
<tr>
<td>Adjusted for age, gender, calcium, parathyroid hormone and 25-OH vitamin D</td>
<td>Regression coefficient</td>
<td>−34.9</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.045</td>
</tr>
</tbody>
</table>

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P1031 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 was 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

<table>
<thead>
<tr>
<th>Number</th>
<th>&lt;20</th>
<th>21–50</th>
<th>51–100</th>
<th>101–250</th>
<th>251–300</th>
<th>&gt;300</th>
<th>Me, UIC, g/l</th>
<th>Me, Thyroid gland volume, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
<td>6</td>
<td>33</td>
<td>23</td>
<td>11</td>
<td>27</td>
<td>157.3</td>
<td>16.4</td>
</tr>
</tbody>
</table>

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 potassium iodide in pregnant women.

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P1032 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.

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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P1033 Clinical importance of incidentally discovered thyroid nodule by carotid artery ultrasonography

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Thyroid nodules are 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 nodules 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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P1034 Thyroid function in relation to pregnancy outcome

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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, thyroid nodules are frequently 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 nodules 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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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 analyze 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 g.w., 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±1.11 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, \( \chi^2 \) 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.

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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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, trametizamide 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. He however, 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 levotyroxine up to 100mcg daily. Due to his difficulty in swallowing, he was started on weekly LT4 injections, which improved his thyroid function and provided stable serum fT4 and fT3 levels.

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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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 (Q1-Q3: 18.6-29.0) vs 25.6 ng/ml (Q1-Q3: 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
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 levotyroxine 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 fT3 and fT4 levels.

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P1037

Evaluation of thyroid nodule, volume and arterial stiffness in euthyroid individuals
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Aim
Overt/subclinical hypothyroidism and hyperthyroidism are known to be associated with cardiovascular risks. There have been no studies evaluating the relationship

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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 euthyroid nodular goitre and 50 healthy volunteers were included. All participants were evaluated by B-mod thyroid ultrasonography (USG) and the individuals in the nodular goitre group were also explored by 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(fT3), free T4(fT4), 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 24th 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. FG5 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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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 <12μg/L and subclinical hypothyroidism (SCH) when TSH was >4 mIU/L. The percentage of ID and SCH were11.87%, 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) mIU/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 prevalence of abnormal elevated TPOAb and/or TGAb, and SCH were 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]. 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. FG5 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

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. FG5 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.

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 in thyroid gland with postive Congo red staining. Surgical pathology revealed the same in addition to a small focus of 0.3 cm FTC. Further evaluation confirmed that patient’s amyloidosis is localized only to thyroid without systemic involvement.

Conclusion

AG should be included as differential diagnosis of rapid enlargement of thyroid gland in HIV patients.

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including the prevention of insulin resistance or the reversal of hepatic steatosis, in the absence of thyrototoxic 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 spectrometric 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.

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 Dövera, 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 was followed up to the middle of 2013.

Results
Overall, 13,876 pregnant women insured by the health insurance company Dövera, a.s. (27.50 market share) who have undergone the first examination 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. 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 thyropathies in pregnant women was found to be 2.19%, while the prevalence of newly diagnosed thyropathies was 5.35%. The overall prevalence of thyrotoxic in the 30–35 year-old women category can be estimated at about 7.54%. From newly diagnosed thyropathies was in the first year after the detection of thyrotoxicity 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 Okmeydani 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 (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 thyrostatic drugs. However, approximately half of patients relapse within two years of discontinuation. It is then necessary to decide whether to re-initiate thyrostatic 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, Protrams - Germany). NGS was performed on MiSeq (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=0.006). 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.

Grant support: MH CR - DRO (EU’, 00023761), MEYS CR (OP RDE, Excellent research and a 2nd FNAB. BRAF analysis was negative in all nodules and all

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 wider (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 sensitivity (Se), specificity, 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 mU/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 Hypoechoegenicity 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 ultrasound 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 ignoring 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. Ultrasoundoneography of the larynx (for her visualisation) 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

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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 (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 ± 11 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 in patients with indeterminate cytology when no BRAF mutation is found from FNAB. The down classification to Thy 2 class is a frequent phenomenon when no BRAF mutation is found from FNAB. The down classification to Thy 2 class is a frequent phenomenon when no BRAF mutation is found from FNAB.

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 suppressed 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 thyroiditis. 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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C reactive protein</td>
<td>132 mg/dl</td>
</tr>
<tr>
<td>ESR</td>
<td>56 mm/h</td>
</tr>
<tr>
<td>WBC/PMNL</td>
<td>15,700/mm³/83.4%</td>
</tr>
<tr>
<td>TSH</td>
<td>0.90 mIU/l</td>
</tr>
<tr>
<td>Free T3</td>
<td>3.78 ng/l</td>
</tr>
<tr>
<td>Free T4</td>
<td>1.72 ng/dl</td>
</tr>
<tr>
<td>Anti TPO</td>
<td>9.0 IU/ml</td>
</tr>
<tr>
<td>Anti Tg</td>
<td>18.14 IU/l</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>500 ng/ml</td>
</tr>
</tbody>
</table>

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 thyrotoxicosis 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 histopathological 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.

References

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P1049

Dependency between vitamin D3 and serum titers of the thyroid autoantibodies in smoking cigarette 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 nicotineism was assessed based on the Fagerstrom 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 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: 8.5 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 autoantibodies. 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 autoimmune 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 17 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.

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 show 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 (45.5%) 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...
Patients had scintigraphy. All yielded suppressed uptake in thyroid bed. Two thyrotoxicosis for correct diagnosis ve management. Subacute thyroiditis must be kept in mind in differential diagnosis of 3.71), ESR 73.3 G free T4 level 2.17 G reduction.

Diabetes mellitus (T2DM) and hypertension (HT) are increasingly becoming a

Talwalkar PG1, Vaishali Deshmukh2, Milind Bhole3 & Rashmi Hegde3

there was high statistical significant difference between group 1 & group 2 & group 2 included 40 subjects ‘cases’ upon which which may replace the need for surgery or radiotherapy. To evaluate the effect of Cryoablation on the size & function of thyroid nodule, Cryoablation is used in a variety of clinical applications, using hollow needles (cryoprobes). Cryoprobes are inserted into or placed 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.

To evaluate the effect of Cryoablation on the size & function of thyroid nodule, which may replace the need for surgery or radiotherapy. Patients and method: 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 was done for subjects & they were sampled for their TSH, free T4 & free T3 levels at start and after 3 & 6 months.

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.e) 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.

Conclusions
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
Post-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 of hypoparathyroidism.

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 6h, 1 day an 1 month postoperatively. Serial 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 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 hypocalcaemia, 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% specificity from 6 h calcium, and 8 mg/dl with 89% of sensitivity and 68% specificity from 1 day postquirurgical calcium. However for the diagnosis of permanent hypocalcaemia, AUC from 6 and 24 h calcium levels was 0.797 and 0.691 respectively.
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-backtranslating method: 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.

Results
The ThyPROes 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. ThyPRO39es 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-backtranslating method: 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.

Objective
Acrinogray is frequently associated with thyroid diseases. In this study we evaluated the incidence, morphology of the thyroid and the influence of surgery, radiation 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 multinoiugl disorder assessed 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 octreotide 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 responsible 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 pituitary-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, HOME index, cholesterol, HDL, LDL and triglyceride levels between groups. The data were analyzed by Welch Two Sample T-test with 95 percent confidence interval.

**Results**

There were no statistically significant difference in glucose levels, as well as in Hba1c and HOME index between groups (glucose 5.249 vs 5.198 mmol/l; P=0.725; HBA1c: 5.55% vs 5.42%; P=0.126; HOME 2.51 vs 2.48; P=0.959). Also, there were no statistically significant difference in cholesterol levels, HDL, LDL and triglyceride 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; Triglyceride 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 intrathyroidal injected steroids for painful lymphocytic thyroiditis**

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Thyroid 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 the case of a 45-year-old woman with Hashimoto’s thyroiditis (HT), and then its name is painful HT (PHT). Painful HT is a rare and poorly documented entity of thyroid pain 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 odalia. Physical examination showed diffusely enlarged 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 intrathyroidal corticosteroid injection was proposed. US-guided injection of 40 mg of triamcinolone was performed in both lobes aimed to the areas of hypochoecenogricity. 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 hypochoegenity 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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**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 controls. 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 cytomfluorometry, using direct immunofluorescence, respectively, on 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 was associated to a co-directional reaction from memory to naive 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=0.37, P=0.012, respectively) and CD3+CD4+CD25+cells (r=0.49, P=0.003, respectively) and CD3+CD4+CD25+Foxp3+ 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+CD25+CD3− lymphocytes (r=−0.49, P=0.036) and the percentage number of CD3+CD4+CD25−cells with CD19+CD25+ (r=0.37, 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 activated B lymphocytes and Treg does not increase 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 thionamine 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 analysis 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. Multivariate regression analysis including length of different thyroid 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 antithyroid 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±4.5 vs. 2.6±3.3 weeks) and subclinical (11±4.2-2.3 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 ≤ 5% and 6–20% of all visits less (P < 0.0001, respectively) frequently (0% and 0% vs 3.4 and 4.8%, respectively) 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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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 oscilometric 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.

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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

<table>
<thead>
<tr>
<th></th>
<th>Before exenatide</th>
<th>6 months after exenatide</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight</strong></td>
<td>112.79±14.73</td>
<td>102.98±14.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMII</td>
<td>44.41±6.63</td>
<td>40.18±6.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.75±1.24</td>
<td>6.74±0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH</td>
<td>2.31±1.09</td>
<td>1.85±0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free T4</td>
<td>0.88±0.13</td>
<td>0.89±0.09</td>
<td>0.888</td>
</tr>
<tr>
<td>Free T3</td>
<td>3.38±0.45</td>
<td>3.50±0.32</td>
<td>0.150</td>
</tr>
<tr>
<td>Anti TPO</td>
<td>64.88±158.33</td>
<td>57.36±141.79</td>
<td>0.072</td>
</tr>
<tr>
<td>Anti TG</td>
<td>11.57±39.05</td>
<td>10.85±37.37</td>
<td>0.120</td>
</tr>
<tr>
<td>CEA</td>
<td>1.89±1.34</td>
<td>1.72±1.03</td>
<td>0.193</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>2.65±1.13</td>
<td>2.65±1.63</td>
<td>0.994</td>
</tr>
<tr>
<td>Thyroid volume</td>
<td>16.42±15.59</td>
<td>14.95±13.28</td>
<td>0.047</td>
</tr>
</tbody>
</table>

**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 peroxidase 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.

**AntiTPO**

**AntiTg**

<table>
<thead>
<tr>
<th>TSH</th>
<th>AntiTPO - AntiTg</th>
<th>AntiTPO + AntiTg</th>
<th>AntiTPO - AntiTg</th>
<th>AntiTPO + AntiTg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01–0.2</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.2–4.5</td>
<td>115</td>
<td>7</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>&gt;4.5</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

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**Endocrine Abstracts (2018) Vol 56**
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. Therefore 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 disorder in Egyptian population
Ahmed Bahaeddin, Alyaa El-sherbiny, Manal Mohsen, Emad Abd e-Ismahen & Mahmoud Naife
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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 prevalence 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 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 compared to the control as well as significant positive correlation between thyroid volume and FBS, fasting insulin, HOMA-IR, 2-h pp BS and HbA1c. 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 χ2/Fisher’s test for proportions).

Results
141 patients, 73.8% women, mean age: 53.3±14.90. 76.6% evaluated by the Endocrinology service prior to the FNA (21.3% previous thyroid pathologies, 87.2% normal function). Symptoms: 88.7% asymptomatic, 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% non-detected). 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% follicular adenoma, 21.8% Hurthle 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 equally 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 significant 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±2.3% vs 34.8±3.6% 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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1Chair and Department of Endocrinology Jagiellonian University Medical College, Krakow, Poland; 2Department of Endocrinology, University Hospital in Krakow, Krakow, Poland; 3University Hospital in Krakow, Krakow, Poland; 4Department of Endocrinology and Metabolic Diseases, the Polish Mother’s Memorial Hospital- Research Institute, Lodz, Poland.

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 mg/l (lower quartile – 61.85 mg/l, upper quartile – 149.0 mg/l). The UIC significantly increased between 2007-2011 and 2018 (median 92.47 mcg/l and 111.45 mcg/l, respectively; P<0.008), 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. In only 17.4% of investigated women, UIC value was within the optimal range of 150 to 249 mcg/l. The 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<0.008), 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. In only 17.4% of investigated women, UIC value was within the optimal range of 150 to 249 mcg/l.

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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P1073

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 µ/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, 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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P1074

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 affected by 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±5.5 kg/m2; 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
**P1075**

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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**P1077**

**Effective complex treatment of endocrinopathies (EO) with hormonal hyperthyroidism resistant 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-Aeg, equivalent of leu-enkephalin) 1mg (per 2.0 0.9% NaCl) SC into the lateral part of the eye, 7 times per day, 4-8 times longer and reduces the aggravation of the symptom by 6%.

Conclusion

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.

**P1078**

**Diminished levels and defective suppression function of Tr1 cells is observed in patients with autoimmune thyroiditis**

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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

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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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P1079
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 colloid 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 was 1.68mIU/L (0.27–4.2), free T4 was 1.01ng/dL (0.9–1.7), free T3 was 2.84ng/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 amyloidosis.

Conclusion
Although amyloid deposition in thyroid is a well known fact in MTC, it should be remembered that it is not a pathological 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 hyperthyroidism. 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 (nicket, histamine, citric acid, cornstarch) and alcohol intolerance. We administered EMPATHY to 150 newly diagnosed hypothyroid patients (150 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=0.001). 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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P1081
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 demonstrate 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 3.4–5.5mg/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 prolactin (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 demonstrated a 3 cm parathyroid adenoma. Histopathophological diagnosis was compatied 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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**P1082**

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 the 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 thyrotropin. 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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**P1084**

Clinical and genetic study of autoimmune 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 iodipathicmyxoedema (PIM), are reoccurring 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 (Ak). Our purpose was search for a combined genetic involved in AITD susceptibility using 33 gene polymorphisms. The Ak pedigree is composed of more than 400 members distributed on 10 generations. Clinical follow-up was performed by applications of the thyroid gland and measurement of both hormone thyroid 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 from 25 to 78 subjects subdivided in 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, IFNγ22, TG and VDR gene polymorphisms have been associated with p-values ranging from 4.10⁻² to 4.10⁻³ when considered with other genes on the same chromosome; giving evidence for gene interaction. The most significant association was found with the MHC region (p=7.15.10⁻³). 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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**P1085**

High endocard 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 endocard, endocardial 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 endocard, 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 endocard levels were higher in the hyperthyroid Graves’ group than the control group (P = 0.08; 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 0.47 (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).

Endocard 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.
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 μIU/ml. 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 μIU/ml. 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 rare form of thyroiditis, and characterized by dense fibrosis of the thyroid 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 hypoparathyroidism approximately 6 months before and she had undergone 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 was 12.7 ng/l (normal range:15–65). Other biochemical tests were normal. Thyroid ultrasound demonstrated asymmetrically 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 kollofen fibrous tissue with mononuclear cells infiltration. There was no evidence of malignancy and resulrly riedel thyroiditis was confirmed as a diagnose. Prednisoln 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 pHb 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...
P1090

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. Review at the first month (n = 20): average reduction of 35.76% (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% reported moderate pain and 5.25% intense pain.
• 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 opposite 'irritable' personality that 'spent extravagantly'. He repeatedly claimed to be 'God’s protection' and responded aggressively to verbal 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 meningococcal meningitis; 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. He was successfully discharged a few days later on levothyroxine and was given a supporting medical letter to help 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.

P1092

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 verbal 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 meningococcal meningitis; 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 thyrotoxyotomy 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 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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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 performed 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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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 extraocular 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 2.1 ±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 varied from 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 (Dferoxamine/Dferasirox) as well as the viral serology.

Results
The prevalence of hypothyroidism is 25%. In 15% it is a subclinical hypothyroidism (1.0 to 1.2) who have benefited from antibody dosing (Ab TPO, Ab TG), while 10% have a central hypothyroidism, it is about two without statural or weight delay having a gonadotropic deficit among them one died by hyperesplenism 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 chelation nor hyperferitemia appears to be risk factors for hypothyroidism with respectively Odds ratio (0.160/2.3/0.73/0.73). 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 study 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 a 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 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.

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.

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 to 10 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-medial CT scan in all cases. A total thyroidectomy was performed in 26 cases and a lobectomy 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.

I131 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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P1097
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 nodule. 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 of the lesion 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 encoding succinate dehydrogenase subunits, SDHD, SDHAF2, SDHC, SDHB and SDHA. Diagnosis of TP is always confirmed postoperatively and differential encoding succinate dehydrogenase subunits, SDHD, SDHAF2, SDHC, SDHB and SDHA. 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P1098
Management particularities of substernal goiter
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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, lansoprazole, insulin, aspirin, atorvastatin, and thiamine. On admission, the TSH was 83 mUI/L, free T4 6.5 pmol/L and free T3 was 1.9 pmol/L; four months earlier, the TSH was 58 mUI/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 para-aneurysmal causes of echocardiography 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.

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P1099
A case of respiratory arrest associated with sepsis induced myxoedema coma
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20th European Congress of Endocrinology 2018
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 (ETHyroid 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 or with antithyroid treatment was 3.07% and 0.14% respectively. The Prev of hypoT estimated by the registered codes 244 and 243 codes for hyperT.

Results
The total 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 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.

Conclusions
1) The Prev of hypothyroidism is higher based on the PHDR than on the DR. The estimate of hyperT Prev is higher based on NPT 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 dysfunctions according to the ICD-9 (and also ICD-10).

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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 two autoimmune thyroid diseases. While transition from GD to autoimmune hypothyroidism has been 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’ ophthalmopathy.

Case 1
A 46 year-old woman with primary hypothyroidism (TSH 169 mIU/ml, normal values 0.5–4.5) treated for 3 years with LT4 50 µg/day, developed hyperthyroidism (TSH 0.013 µIU/m, 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 IFN withdrawal (TSH 65.2 mIU/m, FT4 5.38 pmol/l (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 exophthalmos (TSH < 0.005 mIU/m, FT4 39.6 pmol/l, TPOAb = 434 IU/ml, TRAB 15.5 IU/ml), increased homogenous uptake of 99mTc 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/m, FT4 0.71 ng/dl (0.7–1.8), 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 123I 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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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 peribulbar 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 peribulbar muscle swelling).

Endocrinology was consulted and laboratory showed TSH 0.00 µIU/ml (0.35–4.94), free T4 1.8 ng/dl (0.7–1.8), total T3 133.05 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 20/100 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 20 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 1g 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 8g of cumulative dosing and reevaluation. Patient 2, probably because of the delay reaching proper treatment, needed decompressive surgery.

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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 was 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 16 mm and an elevated serum calcitonin level 29 ng/l (upper limit 21 ng/l). Fourteen women had clinically palpable nodules. Women with thyroid nodules were older (36.6 ± 4.9 vs 32.8 ± 5.0), had higher parity (P = 0.04) compared with women having no thyroid nodules. The subject with TSH also had higher positive rate of autoimmunein (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 gravity 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.

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 34.8(5.4) years and there were 30 nulliparous (51.2%), 49 uniparous (51.1%) and 17 multiparous (gravity ≥ 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 or without gestation. In 50 women, thyrotoxicosis was transient (TRAb-positivity, 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 thyroid 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, P = 0.02) and had higher parity (P = 0.04) compared with women having no thyroid nodules. The subject with TSH also had higher positive rate of autoimmunein (26.9% vs 5%, P = 0.05). No difference in TSH and FT4 was detected throughout pregnancy.

Conclusions
The prevalence of thyroid nodules in 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.

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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 July 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 1.44, 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

We found that TAO patients differed significantly from AIT group in or TAO and the control group among the Caucasian-Polish population. However, there is no statistically significant difference in allele or genotype distribution of (6.60% vs. 1.20%; found significantly higher AA homozygote in TAO group comparing to AIT group.)

Conclusions

There is no statistically significant difference in allele or genotype distribution of

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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 perihperal 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 four of these patients. However the molecular analysis TSHR revealed a known polymorphism (c.361T>Gt; C (rs2975179) in exon 7 of the TSHR gene in a homozygous state in a patient with CH and in a heterozygous state in another patient. No mutation was revealed at that time and the study of other exons is still being analysed. For the remaining case, resistance to TSH due to G protein deficiency was strongly suspected in the presence of pseudohypoparathyroidism. 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 dysmorphia noticed in one case, we will complete with FISH study in search of microdeletion 7q11.23.

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 assess 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 occurrence 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 due to chronic lymphocytic thyroiditis and hypothyroidism. She was on levothyroxine supstitution therapy. Six years ago ultrasound revealed inhomogeneous thyroid, predominantly hypoechogetic with hypoechogetic 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 ultrasoundography: hypoechogetic, 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 μU/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 μU/ml and FT4 1.01 ng/dl at baseline; TSH 32.1 μU/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 Spigren’s syndrome. Medications in addition to L-T4 include hydroxychloroquine, methotrexate and folie acid. In December 2017 she had TSH 58.5 μU/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 metiprednisolone; 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 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 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 fibroblasts (OB) of GO patients.

Background
SOM230 is a somatostatin analog that has a great affinity for the type 1 and type 5 SSRs and inhibits both orbital fibroblasts (OB) of GO patients. SOM230 is a somatostatin analog that has a great affinity for the type 1 and type 5 SSRs and inhibits both orbital fibroblasts (OB) of GO patients. SOM230 is a somatostatin analog that has a great affinity for the type 1 and type 5 SSRs and inhibits both orbital fibroblasts (OB) of GO patients. SOM230 is a somatostatin analog that has a great affinity for the type 1 and type 5 SSRs and inhibits both orbital fibroblasts (OB) of GO patients. SOM230 is a somatostatin analog that has a great affinity for the type 1 and type 5 SSRs and inhibits both orbital fibroblasts (OB) of GO patients.

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 assess 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.

DOI: 10.1530/endoabs.56.P1110
Methods
This pilot study evaluated 10 patients with active MSGO treated with SOM230 compared to 10 patients with MSGO treated with methylprednisolone (MPNS). The patients received 4500 mg of intravenous MPNS or 180 mg of SOM230 for 12 weeks. Clinical endpoints and quality of life (GOQOL) were evaluated at time 0 and at 12 weeks. GO activity score 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 according to overall clinical criteria evaluation and GOQOL; in both groups 50% and 60% of patients improved respectively. Eyelid aperture improved in the SOM230 group compared to the MPNS group although not significantly: −0.71 (−2.45) 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 MPNS 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. DOI: 10.1530/endoabs.56.P1113

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), HSI (Hepatic Insulin Sensitivity Index), WBISI (Whole-Body Insulin Sensitivity Index), IGI (Homeostasis model assessment), HISI (Hepatic Insulin Sensitivity Index), ApoA1, ApoB, ApoA1, lipoprotein (a), free fatty acids, glucose, TC, TG, HDL, LDL, the fasting levels of blood pressure (BP) and BMI were measured. IR markers of IR were used to evaluate the different groups of IR.

Results
After dividing the OGTT sample in 3 groups (IFG-16.6%, IGT-24.2% and IFG-16.6%), we found that patients with IFG had significantly higher levels of triglycerides (TG), ApoB, lipoprotein (a), free fatty acids (FFA), glucose, TC, TG, HDL, LDL, the fasting levels of blood pressure (BP) and BMI were measured. IR markers of IR were used to evaluate the different groups of IR.

Conclusions
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 sodium 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 Peri-TSH syndrome, and c.1708+1T>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=e=2), p.Leu597Ser (n=4), p.Val609Gly (n=2) and p.Asp727Tyr (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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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 sodium 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 Peri-TSH syndrome, and c.1708+1T>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=e=2), p.Leu597Ser (n=4), p.Val609Gly (n=2) and p.Asp727Tyr (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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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 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 Hashimoto thyroiditis is associated with a reduction in antithyroidperoxidase 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 cervical mass accompanied by difficulty in swallowing. Her family history was free of any endocrine or non-endocrine malignant tumors.

Case report
A 70-year old woman with a history of right lobo-isthmusectomy for a toxic multinodular adenomatous goiter, 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 μU/ml and an increased free T4 of 26.6 pmol/l. Thyroid scintigraphy showed a toxic multinodular 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 demographical 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.

Among the heterogeneous population in the UAE, East Asians had the highest prevalence malignancy in examined thyroid nodules. 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.

Conclusion
Cancer rate was higher in males (11.9%) compared to that in females (8.3%). Among the heterogeneous population in the UAE, East Asians had the highest prevalence malignancy in examined thyroid nodules. 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 ±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 that was less than 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 hypoechogeticity 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 hypoechogeticity 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 index for 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 specific 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 (Periuss KV machine with 13 MHz linear transducer).

Results
The outcome of our study shows that malignant micronodules compared the benign 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% specificity 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% specificity, 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 elastoscore 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 BRAFV600E mutation in patients with papillary thyroid cancer
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Background
The BRAFV600E 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 BRAFV600E 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 BRAFV600E 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 BRAFV600E 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 BRAFV600E mutation was 58.3% (95% confidence interval, 49.6-66.6). No differences in patients classified by gender or age groups were found. We could not find any significant association between BRAFV600E 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 BRAFV600E mutation. A significant association between this mutation and the histological variants of PTC was found. BRAFV600E 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 BRAFV600E mutation and the persistence or remission of disease at this time.

Conclusion
BRAFV600E mutation is very common (58.3%) in our population of patients with PTC. In this cohort of patients the presence of BRAFV600E 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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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, autoimmune has been implicated in certain papers. But, reports have been triopolar 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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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.

Material and methods 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).

Results 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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Coexistence of well differentiated, poorly differentiated 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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Incidence of recurrent nerve paresis and hypocalcaemia after total thyroidectomy – A retrospective Analysis

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Keywords: pheochromocytoma, primary hyperparathyroidism and papillary thyroid carcinoma

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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%). IFT/ 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 (≤ 45 years).

Objective
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 ± 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 SUVmax. 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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P1129
Hounsfield unit value has null effect on thyroid nodules at 18F-FDG PET/CT scans
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Introduction
Guidelines suggest that serum basal (nonstimulated) thyroglobulin (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 (Immunoradiometric 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 with structural disease cytologically or hystologically evidentiated. The aim of this study was to verify that sensitive bTg values below FS.

Methods
Patients with DTC treated for differentiated thyroid cancer in 26 consecutive patients

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Introduction
Guidelines suggest that serum basal (nonstimulated) thyroglobulin (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 (Immunoradiometric 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 with structural disease cytologically or hystologically evidentiated. The aim of this study was to verify that sensitive bTg values below FS.

Methods
Patients with DTC from one endocrinology office were included if:

- They underwent total thyroidectomy usually followed by 131I ablative dose.
- 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 < 1 ng/ml (IRMA method) in the absence of localizable disease.
  - Patients with structural disease cytologically or histologically 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 131I. Patients included 16 women, 9 men. 24 were on 131I 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

P1128
Highly sensitive Thyroglobulin assay in monitoring patients treated for differentiated thyroid cancer in 26 consecutive patients

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Discussion
The index of recurrent injury (IRI) was calculated. Patients were monitored 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 131I 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 histologically 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 131I. Patients included 16 women, 9 men. 24 were on 131I 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

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 obviating 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
Follicular thyroid carcinoma with late metastasis to kidney in a patient with elevated thyroglobulin levels of unknown source
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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
Incidental thyroid microcarcinoma diagnosed after total thyroidectomy: 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 (mTC) 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 mTC (max. diam. ≤ 1 cm) in benign thyroid diseases as a potential parameter for surgical decision regarding the type of thyroidectomy.

Patients and 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 mTC was recorded and evaluated according to preoperative diagnosis.

Results
The prevalence of mTC 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 52.3% (40/124 patients) with solitary thyroid nodule-STN and another of 12.8% (6/530 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% (6/137 patients) respectively. Interestingly, mTC was diagnosed in 15.4% (213 patients) with previous thyroid lobectomy or subtotal thyroidectomy; among them there was a case of mTC 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 mTC 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 comorbid thyroid carcinoma, excluding the possibility of future neck re-operation and/or complex long-time follow-up.

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negative group displayed a higher frequency of distant metastases, the volume of PTC was characterized by higher proportion of male patients (37.9 vs 15.5%, \( P < 0.017 \)), and older age at the time of operation (39.3 vs 28.4 years, \( P = 0.005 \)).

Conclusions

The BRAF mutation is an important risk factor for FTC 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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Objective

Predictive factors for the risk of relapse in differentiated thyroid cancer (DTC) are still being discovered. The current retrospective study was the assessment of the prevalence of mITC in patients with non-toxic 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% (90/40 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) focal 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 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.

The prevalence of mITC was characterized by higher frequency of distant metastases, the volume of 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 FTC relapse that may be useful for prognostication during post-operational follow up. DOI: 10.1530/endoabs.56.P1135

P1134

The relationship between clinical, morphological and prognostic characteristics of papillary thyroid carcinoma with BRAFV600E mutation assessed immunohistochemically

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Objective

The BRAFV600E mutation assessed immunohistochemically

Material and methods

Histological and immunochemical 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 mutation status and clinical, morphological and prognostic features of PTC.

Results

Mutant BRAF status was observed in 29 of 74 FTC (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
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 different 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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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 thyrotoxicosis 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 µU/mL, fT3: 5.5 pg/ml, fT4: 2.3 ng/dl) with negative TSH receptor antibody (TRAb <0.7 U/l), and a low grade uptake of $^{127}$scintigraphy in thyroid gland (0%). Ultrasound 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. Diagnosing center 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

<table>
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<th>Lesion</th>
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<th>PR</th>
<th>SD</th>
<th>NE</th>
<th>PD</th>
<th>Death</th>
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<td>7</td>
<td>2</td>
<td>2</td>
<td>4</td>
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<tr>
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<td>5</td>
<td>3</td>
<td>4</td>
<td>6</td>
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<td>16</td>
<td>18</td>
<td>5</td>
<td>9</td>
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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 unrespectable 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 hilar 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 4.4 cm in the left thyroid lobe. One month later, upon referred to our department, abdomen MRI showed enlargement of the hilar 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 (851 851 pg/ml) 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 diarrohoea 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 pg/ml, 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, unrespectable MTC. Further studies comparing combination treatment to Vandetanib monotherapy are needed to validate the efficacy of this approach.

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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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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 University 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) 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. An increase in micropapillary thyroid cancer (<1 cm) from 29.4% to 52.1% 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 diagnosis 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 (post-CT) 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 post-CT (≥2.0 pg/ml). Clinical and biochemical data were recorded. Patients were classified in four groups according to post-CT: group 1: (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>200 (P = 0.005) more frequently. SporadicMTCs had post-CT>200 more frequently than familialMTC (43.6% vs 19.6%, P = 0.019). With increasing post-CT, unfavorable histopathological features and multiple surgeries (n≥2) were more frequent (P < 0.001). Tumor size was larger (median (IQR): 1.0(1.8), 1.25(2.3), 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 group 4 (31.3%, all with post-CT>400). Metastatic disease appeared in 8% of group 1, 18% of group 2, 29.6% of group 3 and 68.9% of group 4 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% and 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: 22.7%, χ² = 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 1131 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 1131 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 < 0.001). 81.1% of patients in the Low Risk category received 1131 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 the probability of absence of disease progression differed significantly between the four groups (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: 22.7%, χ² = 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
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 = 0.0007; 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 outpatient clinic with complaints 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 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 sedimentation rate 34 mm/h (normal < 13 mm/h), elevated anti-TPO antibodies 689 kU/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 node – suspicion of lymphoma or anaplastic carcinoma. Other radiological tests, including abdomen ultrasound, chest X-ray and mammography, evaluating the spread of oncological processes, 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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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

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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 carcinomas (PTCs) in Turkish population

Method
This study reveals that U haplogroup is associated with the susceptibility to benign and malignant 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 also be 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 19x14x45 mm, left lobe was 24x19x55 mm, and isthmus was 2.2 mm. It also showed heterogeneous parenchyma echogenicity for both thyroid lobes, due to the millimetric hypoechoc areas compatible with thyroiditis while there was no nodular appearance. Thyroid stimulated receptor antibody levels were 2.54 UI/0.1-1.5). 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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Determination of the BRAF V600E mutation prevalence 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 macrocarcinaoma 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, 1/2 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 BRAF V600E mutation. Four of 12 macroOVPTC cases had one of the BRAF mutation. One of them was BRAF V600E and the others were BRAF V600E (25%). One of the microOVPTC case had BRAF V600E mutation. When mutation positive tumor samples were compared with mutation negative ones in clinical and laboratory data, no significant difference was found. One of the microOVPTC case had BRAF V600E mutation.

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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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 Hospital 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-recognised guidelines should be implemented to help physicians provide the most appropriate care for these patients.

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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 5×3×5 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 VI lymph nodes to V neck lymph nodes. Immunohistochemistry showed that the tumor stained negative for thyroid transcription factor-1 and thyroglobulin. This is consistent with a metastastic 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.

References


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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 thyroglobuline (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 lymphadenectomy. 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. Of 1069 nodules, 580 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 hypoactive [n = 234 (4.5%)], hyperactive [n = 422 (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 hyperactive 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 14 (4.3%) nodule and benign in 22 (95.7%) nodules. However, 7 (5.7%) nodules had PTC and 1 (0.8%) a 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, 20 (6.0%) with FTC, 10 (3.0%) 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 thyroid nodules smaller than 1 cm

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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; 86.6% 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 infiltrative); 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 biopsy CNB, and there was no 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%. 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 autoimmune hyperthyroidism were excluded. We evaluated the influence of extrathyroidal extension (ETE), positive lymph node (LN), histological 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 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

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
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. Hashimotos'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 thyroideectomy 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’ ophthalmopathy. Her thyroid ultrasound examination showed heterogenous hypoechoic nodule in the right lobe. After medical preparation, the patient had a total thyroideectomy 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 x 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 thyroideectomy 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 Form 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 radiated 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 thyroideectomy 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 Q5L 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%). Preablatice 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 ± 27.82 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 ± 3.6, cumulative dose: 382.6 ± 280 mcgI) a significant decrease of TGL was found (mean 0.672 ng/ml, P < 0.01) in 67% 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 thyroideectomy – so
Thyroid cancer prevalence and pathological features in thyroidectomy patients – five years experience

Objective
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%) unifollicular 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. 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 anaplastic thyroid carcinoma.

Discussion
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 diagnosis 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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2. His sister 46 years had a total thyroidectomy for a suspected nodule Tirads V, anatomicopathological study: 4 cm nodule with a well-differentiated vesicular carcinoma with vascular invasion of the capsule.
3. Another sister 40 years operated as a part of screening with anatomicopathological study: papillary carcinoma in its vesicular variant, encapsulated and bifocal.

A case of familial follicular thyroid carcinoma

Introduction
Familial follicular cell-derived tumours 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, anatomicopathological study: papillary micro-carinoma 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, anatomicopathological 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 anatomicopathological study: papillary carcinoma in its vesicular variant, encapsulated and bifocal.

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.
P1164

The prevalence of concomitant 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 250 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 characteristics 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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Medulillary 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 revealed multiples calcified masses in the liver, consisting in hepatic metastases. In the other hand bone scintigraphy with technetium-99m demonstrated not only multiples metastatic lesions in lumbar spine but also extensive areas of uptake of Tc99 in the liver. Liv 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 (MPC, max diameter ≤10 mm) has increased in recent years. Most have a very good prognosis but some may 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 MPC between 1998 and 2012. Risk stratification system (ATA 2015): 10 high, 34 intermediate and 70 low risk at the diagnosis. Therefore, 38.6% had extrathyroidal 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, 53.18 ± 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 (14.7, 0.0%; P=0.01), capsular invasion (4.3, 44.3, 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 ± 2.0 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 (8.5,00%), 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: surgical reintervention, 5 another radioiodine dose. Thus, 18,4% required at least one more treatment in the follow-up.

Conclusions

In our cohort: younger age, male sex, capsular and vascular invasion, larger tumor size and higher TSH were more prevalent in MPCs 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 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.

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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 of these 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=1439), 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=3376). In these instances no discrete size of the largest nodule was given. Calculations 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 11 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-RT) (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), cerebral-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 ≥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. 0.005±0.05 mL, respectively, P<0.01; 26.9±57.9% vs. 1.7±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 >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 (FNAC) 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 FNAC results.

Methods  
FNAC 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: ≥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(107%), 13 (6.5%), and 9 (5.8%, P=0.007). After FNAC, 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 (≥4 cm) are not at higher risk for malignancy. Surgical decision should be guided by FNAC 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, recurrent 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 (ps-Tg) for recurrent and persistent disease in patients with differentiated thyroid cancer (DTC) 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  
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 ≥ 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, 15.78 ± 12.12 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 ($P > 0.005$).

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
131I-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 $^{131}$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 $^{131}$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 intraaorticaval adenopathies 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 thyroglobulin 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 were included in the study. The wash-out of needle rinsed with 0.5ml of normal saline solution, aspiration biopsy needle washout fluids (FNAB-Tg) in the cases of thyroid cancer.

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 14 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 follicular 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 ± 2.6; thyroid autonomy 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 (16.7%), Intermediate Suspicion (27.9%) and High Suspicion (63.4%). 15 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

**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 mutation: 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 years old woman admitted with fatigue, a serum thyrotropin of 4.6 uIU/ml and a 15 x 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 x 11.8 x 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 thyroglobuline 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 nodules was reported as 17 x 14 mm mixed medullary and papillary thyroid carcinoma. Immunohistochemistry was positive for TTF-1 and calcitonin, and in focal areas thyroglobuline, CK-19 and HMGB-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 cytological malignancy diagnosis**

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**Objective**

The aim of our study is to assess 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 cytological 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 autoimmunity (antithyroglobulin 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 or 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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The role of thyroid imaging, reporting and data system scores – ACR TI-RADS in thyroid nodular disease – our experience

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Introduction

Lithium is the most efficacious and most tolerate therapy for acute and maintenance therapy of bipolar depressive disorder. Lithium use is associated with an increased incidence of hyperparathyroidism (4.3–6.6%) and have a female preponderance. Bilateral neck exploration was the most common surgical finding. High cumulative result leads to higher TR level and the higher probability of malignancy, which provides recommendations for either 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 TR of 3.43. From a total of 65 patients, 72% showed benign cytological findings, whereas 9% were in the AUS or AUS/FUUS category (ataxia 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 represented with 33.3%. Vascularization of nodus type 2 had 34% and 8% had type 4 patient with benign findings, while with AUS findings, 59% 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. DOI: 10.1530/endoabs.56.P1181

Pediatric thyroid cancer is associated with more aggressive phenotype and more frequent RET/PTC rearrangements compared with the adult patients

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Introduction

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 promoter C228T and C250T mutations by CEQ8000 and BRAF and RAS mutations by Nextera XT kit with MiSeq. RNA was used for detection of RET/PTC 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/PTC6. In 8 years old boy with aggressive classical variant of PTC (T4N1M0) 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 tumourogenesis 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 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 statistically 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. The lesion was 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 levothyroxin 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 FLT3 mutation found in the follicular thyroid cancer. 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 FLT3 mutation (3' end of exon 13) in 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 suprathyroid median line, with some phlegmon signs. Laboratory examinations include: TSH 3.21 aU/ml, T4L 1.0 mg/dl and Anti-TPO/AbTG (c). Cervical ultrasonography revealed homogenous thyroid gland with normal dimensions. RTL: hypochogenic nodule with defined edges of 9×7 mm soft consistency to elastography. In the anterior central side of the neck, suprathyroid cystic image with sediment and thick calcifications was observed, measuring 48×39×59 mm, with a volume of 58.3 ccm. CT: encapsulated, lobulated and bilobed cystic lesion with small internal calcifications measuring 33×30×15 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 demonstrated 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 neoplastic 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 presumable in 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 55.2 ± 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 nodule 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 EEU-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-suspicion categories which should warrant FNA in most cases.

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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 – atypia 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 – 1 Ci. 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 thyroidectomy (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 55×26 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 metastases. 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 to 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 21×18×17 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 duct cyst, mediastinum, and ovary. They are usually diagnosed only after excision of the lesion, with a more frequently papillary pattern. However, follicular, mixed, Hurthle 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

Retrospective 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 mediullary 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 (SD 13.7) years, (83.3% women). Histologic diagnosis: 7 papillary thyroid cancer, 4 poorly differentiated follicular thyroid carcinoma and 1 Hurthle cell cancer. Distant metastasis at diagnosis were present in 25% of patients. In the other 75% median time to metastasis diagnosis was 24 (IQR 12) months. Seven patients had more than one metastatic lesion site. Median time from diagnosis to distant metastasis to TKIs initiation was 24 (IQR 78) 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 (41.6%), 1 (8.3%), 1 (8.3%) and 5 (41.6%) 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/hyper-elexa (83.3%) followed by cutaneous AE (58.3%), diarrhea (41.6%), hypertension (16.6%) and mucositis (16.6%). Cutaneous AE occurred 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 (IQR 36) 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 Ibn 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.

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(91.05%) 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 AJCC 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.

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).

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, 16 - 61 month). 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%; 16/3 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

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.

Material 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. Radiotherapy (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) were T2 9 cases) T3 (3 cases) T4 (2 cases)
P1197

Amiodarone – thyrototoxicity and thyroid cancer

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Introduction
Although thyrototoxicity 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 thyrototoxicity 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 paroxysmic 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-homogeneous 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 I 131 scintigraphy of the thyroid revealed non-homogeneous distribution of I 131 with areas with no captation in both thyroid lobes. The patient underwent external radiation therapy and chemotherapy. Since 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 Roch 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.

Conclusions
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 profile indicated subclinical hyperthyroidism with suppressed TSH=0.09 mU/L (N=0.5-4.5 mU/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 hypoechogenic macronodule, apparently non-vascularized, of 6.3/5.5 cm, and a left thyroid lobe with a hypoechogenic 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 1.31/0.4, 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 4.2/8.6 cm. Also, a right adenopathetic 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.

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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 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 Clínica 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 were follicular adenoma, 33 (41%) was benign nodules. TSH level was significantly higher in patients with thyroid cancer compare with follicular adenoma and other benign nodules. 30% patients with thyroid cancer had TSH > 2.5 µIU/ml and only 18% with follicular adenoma, 12% with other benign nodules had TSH level > 2.5 µIU/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 4.2±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.

Conclusions
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 ratios(PR), and statistical differences were 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 1.01 – 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 1.04 – 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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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 56.5 ± 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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Association of thyroid papillary carcinoma and 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 confirmed the diagnosis of papillary thyroid carcinoma in three patients.

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**

Hypertension in 71-yr old women with heterogenic left adrenal mass with signs of bleeding inside.

**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 the endocrine and nervous systems. They are most commonly occur in the intestine and are graded histologically according to markers of cellular proliferation. GI 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 U/ml (Ref. 28–185) and serum chromogranin-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, megablastic 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 antiantibodies, and she was diagnosed with polyglandular syndrome Type 3 with gastric NET. Three months later the patient underwent a white light endoscopy. The gastritic biopsies revealed: atrophic gastritis with intestinal metaplasia and possible micromalignancies in the body of the stomach. Pathology report revealed linear and nodular hypervascularia 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 an obstruction of lower bile duct. Endoscopic biopsies from the ulcerated region, and endoscopic retrograde biliary drainage (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 20x18 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 chemotherapy for the patient might be platinum-based regimens. Because the patient was 83-year-old, postoperative chemotheraphy 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/m2 and Kt 67 was 50%. First-line chemotherapy for the patient might be platinum-based regimens. Because the patient was 83-year-old, postoperative chemotheraphy has not performed. Post operative course was uneventful and the patient discharged 24 days after the operation.

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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 be 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 creatinine level rose from 1.33 to 2.45, with hypotension, hyporenatremia, pretilial +++, ++ +++, + +++, + +++, + +++, and shortness of breath. The patient was evaluated for 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 2×100 mg of octreotide SC dose was started treatment was started. The patient recovered from hypoglycemia with this treatment, but sudden increase in creatinine level and shortness of breath 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 sometimes.

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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 a rare report. We report a case of 73 year old woman 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 period. The patient had a history of type 2 DM for 10 years. Although oral antidiabetic drugs are stopped, hypoglycemic episodes persistently occurred. 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. Chromomarin A was >500 ng/ml (referance 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 lymph 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. Prednisolone 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 injections 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 successful 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 disapproval. 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 or paragangliomas are rare neuroendocrine tumors. Although mostly sporadic, about 1/5 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) 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

Fifty 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, hypercortant, 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 μg/24 h (5–20), noradrenaline 31.7 μg/24 h (15–80), vanillylmandelic acid (VMA) 5.2 mg/24 h (1–4.6) and homovanilllic acid (HVA) 4.2 mg/24 h (<8.3) in 24-h-urine. The scintigraphy with 113I-norcholesterol documented nonfunctioning lesion, aspiration biopsy was suggestive of pheochromocytoma and scintigraphy with 111Indium-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 and scintigraphy with I123-MIBG was negative. 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 2×100 mg of octreotide SC dose was started treatment was started. The patient recovered from hypoglycemia with this treatment, but sudden increase in creatinine level and shortness of breath 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 sometimes.

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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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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 hydronephrosis 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 the 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 constriction of the internal ureteral sphincter, excessive sympathetic stimulation can cause urinary retention and hydroureronephrosis. This case report draws attention to the patients presenting with adrenal mass and unexplained ileus, constipation and non-obstructive hydronephrosis. This case of phaeochromocytoma 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 phaeochromocytoma: a case report
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Phaeochromocytoma (PCC) is a rare neuroendocrine tumor, mainly sporadic, many cases are discovered incidentally by computed tomography or magnetic resonance imaging of the abdomen. Malignant phaeochromocytoma 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 cm in the right, 3.8 cm in the left. Preoperatively blood test confirmed PCC and a right adrenalecctomy was performed. After histological evaluation phaeochromocytoma 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 mmol/L, n – 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, ilium 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, paratracheal 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.
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 adenocortical 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 9.5×15×12 cm heterogeneous 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. Adrenalecctomy was performed. Histopathological 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 classified regarding their biological behavior by their histological features according to the Lin-Weiss-Bisceglia system (LWB). The existence of at least one major criterion defines a malignant oncocytoma (>5 mitotic figures per 50 hp fields, atypical mitoses or invasion of 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 than 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, frequency and parameters needed to follow-up on patients with oncocytic neoplasms of borderline malignant potential.

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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 constitute 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/m²) 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 celiacic mass measuring 34×32 mm. Transhepatic 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 an echodenscopic 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, phaeochromocytoma, renal cell carcinoma and/or cysts and pancreatic neuroendocrine tumor and/or cysts.

Methods
From a parental generation whose clinical data are unavailable, two sisters from 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 siblings 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 sibling (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 Cushing's disease. 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
Present report supports the relevance of RET testing in patients with pheochromocytoma without evident medullary thyroid carcinoma. The patient harboring RET D631Y mutation with long history of 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 cm and 2.7×1.5×2.2 cm. 123I-MIBG scanning showed increased uptake in the right adrenal. Patient’s calcitonin level was normal 4.59 μg/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, immunohistochemistry staining revealed the SRTR2 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). Exploration of the cause of hypothyroidism concluded to a destructive cause. Thyroglobulin < 0.2 ng/ml undetectable. Antibodies (Ab) anti thyroperoxidase and Ab Thyroglobulin are normals. Cervical Ultra sound find a normal overall volume of 10 cm³ 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 1 month 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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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, weight 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 3.5–5.0 mmol/l). The patient had normal renal and hepatic tests. Thyroid function and serum morning cortisol levels were normal. IGF-1 and IGBPBP3 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 IGBPBP3 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 continuous subcutaneous hydrocortisone infusion (CSHI)
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We recently reported the impact of continuous s.c. hydrocortisone infusion (CSHI) on weight, patient AddGoQoL 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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Abstract

Ganglioneuromes are benign tumors from neural crest cells, mostly located in the posterior mediastinum and retroperitoneum, and are rarely localized in the adrenal gland. We report the case of a patient. 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 dexamethasone 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.

**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 could 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 anatomicopathological 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.

**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 dexamethasone 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. The GN 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.

**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 atrauma) 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. 18F-FDG PET/CT showed numerous bone metastatic lesions of spine and ribs. No tumor lesion took up 111In-MIBG and somatostatin receptor scintigraphy is planned to decide if the patient is suitable for peptide receptor radionuclide therapy 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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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, endolympathic 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 MBG scintigraphy confirmed bilateral pheochromocytoma (PCC). Another diagnostic VHL sign—cyts 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 nmol/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. Diagnosis of VHL was made based on clinical findings. The multi-disciplinary team decided to remove left adrenal gland because the size of the left adrenal tumor was four times larger and in 24 h CT it had more intensive radiomuclide 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.

Conclusion
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 secretation 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 1–100 ng/ml) reaching 78,870 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 phenoxbenzamine dose was increased. However, his condition worsened and a right hemicolectomy with ileostomy was performed, which proved to be ineffective as well. Intravenous phenolamine perfusion and laparotomy were then initiated. Unfortunately, due to limited availability of phenolamine 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 α1- and β2-receptors, 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 α1-blockers, in particular intravenous phenolamine, and eventually methylxyroisine, may be useful in relieving this complication which can have a poor outcome.

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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 4.5×5 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 tumour had a high density in native CT sequences (48 Hounsfieild Units). MRI showed T1 iso-intensity and T2 hyper-intensity, as well as lymph nodes of the cervical trunk. 24-h urine metanephrines were 5 times higher than the upper limit of normal range. 11C-MIBG-scan was negative. The patient also fulfilled clinical criteria for type 1 neurofibromatosis (NF-1, Von Recklinghausen disease). After preparation with αβ-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 11C-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 secretation product. As disease progressed, multimodality treatment was required: alfa end beta adrenergic receptor blockers, α-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 78,870 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 phenoxbenzamine dose was increased. However, his condition worsened and a right hemicolectomy with ileostomy was performed, which proved to be ineffective as well. Intravenous phenolamine perfusion and laparotomy were then initiated. Unfortunately, due to limited availability of phenolamine 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 α1- and β2-receptors, 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 α1-blockers, in particular intravenous phenolamine, and eventually methylxyroisine, 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 dysgeusia, slimming quantified at 14 kg over 15 days, asthma and anorexia. The examination found a conscious patient, a BMI at 20 kg/m², 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 TI-RADS 3 and a negative calcitonin, thoraco-abdomino-pelvic CT showed duodenal lesion associated with ganglion masses, retractive 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 haitic, then bronchial, colic and gastric. Biologically, indicating paraneoplastic endocrine secretions such as flush syndrome. The most NETs are rare tumors but must be evoked especially in the presence of symptoms above the upper lobe of the right kidney, measuring 34×45×42 mm. She has been without symptoms. MSCT of abdomen revealed tumor mass in the right adrenal gland that measured 35×45×44 mm. The catecholamine levels were normal. Laporoscopic 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 111-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 blockade with Na-perchlorate had been started 30 min before injection of I-131-MIBG and continued during next five days. I-131-MIBG was intravenously applied 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 pathohistological confirmed metastatic neuroblastoma in lymph 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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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), although 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 excrion 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 hypoechoic focal lesion with increased vascuarization 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 misleading 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.

A 55-year-old woman underwent for regular abdomen ultrasound examination. Sonography revealed inhomogeneous, predominantly isoechoic tumor mass above the upper lobe of the right kidney, measuring 34×45×42 mm. She has been without symptoms. MSCT of abdomen revealed tumor mass in the right adrenal gland that measured 35×45×44 mm. The catecholamine 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 blockade with Na-perchlorate had been started 30 min before injection of I-131-MIBG and continued during next five days. I-131-MIBG was intravenously applied in dose of 37 MBq (1 mCi).

Results
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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 evaluation 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 mediastic 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, concerning 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. Notwithstanding, 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 relies on a treatment.
- Elicits a burden of cardiovascular complications estimated at fivefold that of essential hypertension with comparable blood pressure.
- 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 50,000 in order to proceed to resolving 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 exceedingly complex and costly. General implementation of the present guidelines is patently inviable, hence it is unsurprising that

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**EP29**

Patient with post-surgical hypoparathyroidism 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 hypoparathyroidism treatment is to relieve symptoms and to normalize levels of calcium and phosphorous. 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 arrythmias. Goal is to show a patient with post-surgical hypoparathyroidism, severe hypocalcemia, hyperphosphatemia, hyperthyroidism, tetany, syncope and LQT interval.

Materials and methods
A case report of 60 years old woman who has developed post-surgical hypoparathyroidism and hypothyroidism 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 (sonized 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 with high parathyroid hormone levels. The demographic characteristics, 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 mmol/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 mmol/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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Interventional study to compare two regimens of vitamin D supplementation

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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.

Materials and methods
This is an interventional study: Patients attended in our clinic during May and June 2017 with 25-Hydroxvitamin D below 30 ng/ml were consecutively selected and supplemented with two types of regimens: 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 hydroxifolate 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 regimen 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/Obezity/dyslipidemia, 35% Thyroid/Pituitary disease, 17.5% Malnutrition. Baseline mean 25-Hydroxvitamin 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 regimen 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 regimen with 16,000 IU of calcifediol weekly during 1 month and then monthly during 5 months achieve 100% of vitamin D sufficiency (25-Hydroxvitamin D > 30 ng/ml).

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 isolation 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.

EP34
Bone mineral density and polymorphisms of the estrogen receptor gene, vitamin D receptor gene and collagen type I gene

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Objectives
The aim of this study was to analyze the prevalence of some polymorphisms of the CTR-Alu, VDR-FokI, COL1A1y ER-alpha gene, (involved in bone metabolism),
in our population. And evaluate the association of these polymorphisms with bone mineral density.

**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. The significant association between polymorphisms and bone mineral density. The prevalence of the polymorphisms in our study was: $Gen\ COL1A1^{PS1}:59\%\ SS, 20\%\ Se, 21\%\ se; Gen\ CTRAL1:5\%\ AA, 41\%\ Aa, 54\%\ aa; Gen\ ESR1PPIII:36\%\ Sp, 35\%\ Pp, 29\%\ pp; Gen\ ESR1XXB1:10\%\ XX, 48\%\ Xx, 42\%\ xx; Gen\ VDRBMSI:11\%\ BB 44\%\ Bb, 45\%\ bb; Gen\ VDRFFOKI:40\%\ FF, 45\%\ Ff, 15\%\ ff. No polymorphisms were associated with low bone mineral density ($P>0.05$). Only an association was found for the PolEStRXX gene and the presence of osteoporotic fracture after menopause ($P=0.02$).

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 hypoglycemia. These patients’ knowledge of the defining value of hypoglycemia and severe hypoglycemia, signs of hypoglycemia, and their behavior were assessed if they experience hypoglycemic discomfort.

**Results**

The mean age of the patients was 68.6 $\pm$ 11.2 years. The average body mass index (BMI) was 37.9 $\pm$ 3.3 kg/m². Diabetes was insulin-dependent in 100% of cases that had been on the move for 16.8 $\pm$ 8.3 years on average. Diabetes was poorly balanced in all patients with mean HbA1c of 9.2 $\pm$ 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 hypoglycemia was defined as glucose lower than 0.5 g/l, by 80% 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 hypoglycemia. 38% only know that if hypoglycemia recurs, they may not be felt anymore. 84% do not know that severe or repeated hypoglycemia can cause neurologic sequelae. 80% resume 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 hypoglycemia.

**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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Endocrine Abstracts (2018) Vol 56

**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/m². 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, telmsartan 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/m². Complementary investigation revealed A1C 10.7%, C-peptide 1.4ng/mL (1.0–7.6) and negative islet autoantibodies. Metformin was suspended due to hyperfucactadicaemia 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.

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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/m2; 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 36.85 ± 7.84%, P = 0.057; Android: 45.35 ± 8.06% vs 44.34 ± 7.15%, P = 0.393; AG 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 ± 5.54%, P = 0.384; Android: 46.38 ± 7.71% vs 46.56 ± 7.28%, P = 0.389; Gynoid: %: 43.14 ± 6.95% vs 46.10 ± 5.32%, P = 0.021; AG Ratio: 1.08 ± 0.15 vs 1.10 ± 0.16, P = 0.03; 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 AG 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 T2D women (r = 0.18; P = 0.023), however no correlation was found with the duration of the disease, level HbA1c, the T2D 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), AG/Ratio (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 enterprise 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 questionnaire.

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/m2 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 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/m2), 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/m2, 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 responders 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 49% 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 imbalance 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 than 5 years, HbA1c up to 9.0%, non-smokers, signed IC. LAKK-M was used. The value of perfusion was measured M, α- 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 ± 5.4 with an average HbA1c of 8.17 ± 0.36% and vitamin 25 (OH) D of 21.4 ± 3.4 nmol/l. Group II included 12 patients (6F), the mean age was 51.3 ± 5.9, HbA1c 8.35 ± 0.63%, 25 (OH) D 20.9 ± 4.1 nmol/l. Group III included 14 patients (7F) HbA1c 7.32 ± 0.19% and 25 (OH) D 27.1 ± 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 ± 1.37, 12.36 ± (2.51), 12.36 ± (1.92), α = 5.32 ± 0.79, 4.44 ± 1.05, 7.1 ± 0.38, Kv = 11.36 ± 1.59, 10.64 ± 2.93, 15.44 ± 2.49. After 24 weeks HD we found no changes in group I-HbA1c 8.06 ± 0.39%, 25 (OH) D 24.68 (P = 0.07), M = 10.30 ± 1.14 (P = 0.08), α = 4, 98 ± 0.56 (P = 0.05) and Kv = 11.82 ± 2.38 (P = 0.87). Significant differences were found in group II: HbA1c decreased to 7.42 ± 0.73% (P = 0.023), 25 (OH) D increased to 60.88 (P = 0.003), All parameters were improved microcirculation M = 19.69 ± 2.52 (P = 0.003), α = 6.05 ± 0.93 (P = 0.005), Kv = 13.36 ± 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 diabetes 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 ± 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 ± 8.3 mg/dl and mean HbA1c was 6.3 ± 0.2%. Thirty DM patients were using metformin treatment in a dosage of 2 g/day.

Results
The mean age was 59.0 ± 10.8 years in diabetics and 47.2 ± 16.8 years in nondiabetics. Mean BMI was 27.8 ± 6.2 kg/m² and mean vitamin B12 level was 139.3 ± 29.2 pg/ml for whole population. Mean vitamin B12 level was found to be low in diabetics compared to nondiabetics (131.2 ± 30.6 and 143.5 ± 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 4, 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 absorption 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 ± 32.5 vs. 138.6 ± 28.7 pg/ml, respectively).

Discussion
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 plasmathyrotrypin levels associated with degree of obesity and metabolic syndrome in euthyroid obese patients? Ocan Sefa Bakiner1, Emre Bozkirli1, Gulhan Cavitak1, Kursad Oszahin2 & Melek Eda Ertorer1
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We aimed to observe the association between degree of obesity and metabolic syndrome and plasma thyrotrypin 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 thyrotrypin levels were compared to normal weight control group. No association was shown between the presence of metabolic syndrome and plasma thyrotrypin levels for both all patients and subgroups. Also there was not any association between each component of metabolic syndrome and plasma thyrotrypin levels. In conclusion, we did not found any significant association between plasma thyrotrypin 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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Craniohypophyseal tumors that in a high percentage of patients leads to damage of periventricular nucleus and suprasachiasmatic nucleus, what leads to the development of hypothalamic obesity. Hypothalamic obesity is associated with numerous metabolic disorders. Regardless of the numerous studies of new therapeutic approaches, there is still no official approved effective (pharmacological or bariatric) treatment for hypothalamic obesity. Liraglutide is a 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 craniohypophyseal as a 51 year old after sudden headache attack, followed by vomiting and unconsciousness. CT scan showed an expansive, suprasellar cystic tumor of dimension 25X27X21 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: Craniohypophyseal papillar, WHO grade I), endocrinological testing showed panhypopituitarism and uncontrolled diabetes (HbA1c 10.3%) with obesity (BMI 31.9 kg/m2). Replacement therapy with hydrocortisone, 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 weight was observed 6 months. The phato was achieved on BMI 26.8 kg/m2 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/m2 and 133 had longitudinal sleeve gastrectomy. The mean BMI loss was 15.92 kg/m2 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 hungerliness, 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/m2, P=0.0049; 13.6 vs 14.4 kg/m2, P=0.0002; 12.2 vs 14.3 kg/m2, 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 gastrectomy 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 circumference, 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 measurements 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 preoperative waist circumference.

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 1.99 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 MRT, 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 thymus tumor. The patient underwent radiotherapy. 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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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 milk 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 pseudocysts were formed. The patient had undergone a gastro-entero-anastomosis for the biliary-digestive compressive syndrome caused by pancreatic pseudocysts. Further hospital admissions occurred because of gastro-esophageal varical bleeding. Indeed, pancreatic pseudocysts 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 elective management of hypertriglyceridemia would potentially decrease the occurrence 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 with colorectal cancer at the age of 46 years old.

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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 December for 2017, 20 patients were observed with DM 2, men – 9, women – 11; 54.5 ± 1.5 m/s/61.6 ± 1.8 w yrs 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, dislipidemia (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 IIT and CT among risk factors of symptomatic hypoglycemia we found diabetic encephalopathy I-II.

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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 I group received 2000 IU/day of cholecalciferol for 16 weeks, the II group of 24 patients continued antihyperglycemic and antihypertensive treatment. BMI, glomerular filtration rates (GFR), hemoglobin A1c (HbA1c) were estimated. Inclusion criteria: type 2 DM patients with HbA1c ≥7%; GFR >90 ml/min/1.73 m², 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±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/m², HOMA – (6.3±2.31), HbA1c – (7.8±0.85%), the baseline UAER – (68.4±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 I 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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EP58

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).

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EP59

Gender differences in patients with coronary heart disease and diabetes. A retrospective study

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DO: 10.1530/endoabs.56.EP59
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 diabetes 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 57.53 years ± 11.22. The average BMI was 29.45 kg/m² ± 4.55. Diabetes was type 2 in most cases, poorly balanced in all patients with an average HbA1C of 10.23% ± 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, trolley bacterial infections, amputations, gangrene 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 including 168 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 (retniopathy, neuropathy, renal insufficiency, ischemic heart disease). Analyzis was 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 hypertglycemia in 58.3% of cases (P < 0.02), and hypoIDLemia in 38% (P < 0.001).

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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Introduction
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.

Material and method
is to evaluate the knowledge of diabetic patients on this entity.

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 hypertglycemia in 58.3% of cases (P < 0.02), and hypoIDLemia in 38% (P < 0.001).

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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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 previous 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/m²), 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 ashenia 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 Type 2 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 (ranging 60–84 years). Sex ratio (M/F) 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=0.001). 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 microflora 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 microflora (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 microflora and cytoplasmic and mitochondrial arginase isoforms (A1 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 Staphylococcus aureus was also observed in T1DM, which may compete with the gut beneficial bacteria. Of note, E. coli and Clostridium spp play a protective 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 NO/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 glycaemia. (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 unrecognized episodes requiring hospitalization. She tests her glycaemia 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 (I pro-2 Medtronic (USA) system was carried out for a detailed study of glucose curves for 6 days. The increase in glycaemia 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), liability index LI 3.83 (mmol/l)/h (4.7), the continuous overlapping net glycemic action CONGA 1.139 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 glycaemia, 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 (SGLT2). Its mechanism of action is glycoursia induction, associated with lowering glycaemia. 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, eu glycaemic 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 mEq/l), acute renal failure (creatinine: 1.86 mg/dl, basal creatinine 0.5 mg/dl), leukocytosis (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 use of intravenous fluids (4 l/day) and of dapagliflozin (40 mg 2id). 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.

**Case report**

A 59 years old female patient had morbid obesity (BMI 41 kg/m²) and type 2 diabetes mellitus diagnosed 17 years ago, chronically poorly controlled (HbA1c > 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 coronaryaropathy with anterior AMI diagnosed five years ago and successive heart failure with preserved ejection fraction and paroxysmal 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 Lisinopril 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 HbA1c 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 HbA1c 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 controlled glycemic targets in patients with multiple cardiovascular risk factors. The new drugs such as the GLP-1 agonist receptors can be a better alternative and sometimes allow withdrawal of insulin.
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 systemic 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 cesarean 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). Orbitophaty 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/m²) 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. 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/m²) 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.

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.

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 hypertriglyceridemia 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%.

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, transfers to the ICU with diagnosis: Diabetes mellitus newly diagnosed. Diabetes ketoacidotic coma II. Concomitant: Left-sided pneumonia.

Objective
Cussman’s breath, 36-minute. Pulse 128/min. BP 100/60 mm Hg. Glycermia 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. Langs: left-sided upper-lobe large focus. Acinetobacter baumannii pneumonia 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 inadequacy to glycermia. 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 glycermia 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 0.07–0.05–0.04 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; for poor glycemic control in patients with diabetes due to bacteria and their byproducts in the inflamed periodontal tissue constituting a chronic source of systemic challenge to the host, increases the risk of diabetes-associated complications and possibly even of its onset. Some studies suggest mechanisms by which oral bacteria may contribute to development of obesity by increasing appetite 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 ability 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-being. It is still not sufficiently communicated within the medical community, because the periodontal disease is still considered as the concern of only dentists. Physicians and dentists need to be aware of the relationship between periodontitis and diabetes and take adequate steps to minimize 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 health will challenge 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. Case presentation

A seventy-three-years-old man with diabetes mellitus who was operated due to orbital trauma a month ago. Periocular cellulitis and diabetic ketoacidosis 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 Amphotericin B 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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**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 obesity. Diabetes and obesity promote the occurrence, the progression and the severity of periodontitis. Conversely, periodontitis was shown to be a risk factor for poor glycemic control in patients with diabetes due to bacteria and their byproducts in the inflamed periodontal tissue constituting a chronic source of systemic challenge to the host, increases the risk of diabetes-associated complications and possibly even of its onset. Some studies suggest mechanisms by which oral bacteria may contribute to development of obesity by increasing appetite 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 ability 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-being. It is still not sufficiently communicated within the medical community, because the periodontal disease is still considered as the concern of only dentists. Physicians and dentists need to be aware of the relationship between periodontitis and diabetes and take adequate steps to minimize 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 health will challenge 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 case of quickly silently growing colorectal cancer of colon ascendens was described, which in one year resulted in bilateral postanal obstruction, which led to chronic metformin overdose and sudden severe lactic acidosis.

**Conclusion**

A case of quickly silently growing colorectal cancer of colon ascendens was described, which in one year resulted in bilateral postanal obstruction, which led to chronic metformin overdose and sudden severe lactic acidosis.

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Parapharyngeal abscesses of dental origin in diabetics

EP79

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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 parapharyngeal 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-inflammatory was given in 3 cases. The examination noted in all cases a trismus, a bad dental state and a puncture return. Outpatient treatment with antibiotics and anti-inflammatories was given.

Conclusion
Diabetes mellitus is a health problem worldwide. The most common causes of abscesses in the head and neck region are odontogenic infection, tonsillitis, and acute pharyngitis. Parapharyngeal abscesses are rare at dental origin. Treatment of parapharyngeal abscesses of dental origin is surgical, medical, and antibiotic therapy.

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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).
2. 43 year old lady was admitted with glucose of 38 mmol/L. Her HbA1C was 160 mmol/mol. She was treated as hyperosmolar hyperglycaemic state (HHS).
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.
4. 36 year old lady was admitted after general decline in health. She had a glucose of 73.3 mmol/L and was acidic. She was treated as DKA.

Discussion
Olanzapine, clozapine and amisulpride are known as novel 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.

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EP78

Childhood granuloma annulaire first sign of diabetes mellitus: case series

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Granuloma annulare (GA) is a self-limiting 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 it is not a rare condition seen in adulthood. Aetiology and pathogenesis of GA are still unknown, although variable associations have been reported, during last decades, in previous reports of diabetes mellitus. Controversial association between GA and diabetes mellitus has been established in the literature. We present cases of GA diagnosed in children (case reports in the last decade with diabetes mellitus, thyroid disorders, HIV infection, malignancies, tuberculosis, Epstein Barr and hepatitis C virus infection or drug administration). The presence of GA in children with diabetes mellitus may be a marker for new diagnosis or continuation of disease. We report 3 cases of GA in children with diabetes mellitus.

Conclusion
The importance of childhood diabetes mellitus is rarely possible, though useful. The presence of childhood diabetes mellitus in children may be a marker for other conditions.
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 non-observance, 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 antihypertensive 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 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), oocactus (12), ORL (5), lung (4), psosas (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, pseudomas aeruginosa (16.6%) for corneal abscess and specificity of Aspergillus fumigatus in the case of a complicated pansinusitis 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.

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 ketonic decompensation (60.8%). Localizations were: Brain (1), ORL (9), eye (12), lung (4), mediastinal (1), liver (19), psosas (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%), pseudomas aeruginosa (10.8%), staphylococcu and/or streptococcu (39%), a specificity of Aspergillus fumigatus 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 Klebsiella 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 hyperglycemia and absence

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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 22nd 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/m² 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 glucose metabolism.

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 ± 7.5 years and 53.1 ± 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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EP85
Impact of magnesium deficiency on chronic complications of type 2 diabetes
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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/min; systolic blood pressure: 130/70 respiratory rate: 14/min. Temperature: 37°C. Physical examination: erythematous xanthoma on the exterior 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: 23.8 Mm/l; SaO2 98.0% ) CBC Hb:11.6 g/dl, TLC: 5.8000 x 10⁹/l, PLT: 245,000 x 10⁹/l, CRP: 132 mg/dl;Chol: 464 mg/dl, LDL: 257 mg/dl, HDL: 25 mg/dl, TG: 9086 mg/dl; aniongap: 1120 ΜΗ, Lipase: 370 ΜΗ/μαλλ, CRP: 141 mg/l, K: 3.8 mg/dl, Urea: 34 mg/dl; Creatinine: 5 mg/dl, 24 h. Urinary PTE: 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:5.5, TSH:1.7, FT4-1, ACTH:12, Cortisol AM:8; GH:0.1 mg/l. Abdominal ultrasonography showed: Enlarged Bright hepatomegaly 16 cm, 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 humoral mixed ulcers of hypo echoic pattern. Echocardiography: Concentric LT ventricular hypertrophy. MRI brain (Bulky pituitary gland showing a focal central bulge (0.4 x 0.1 x 0.7). Renal biopsy: Minimal change glomerulonephritis. After 3 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 fenoibrate 4 months later she came for follow up.

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 hyperglycaemia or acidosis with no evidence of pancreatitis. To our knowledge, there are few reports of patients who developed pancreatitis and DKA during treatment with antipsychotics. We present a case of a patient who developed such life-threatening conditions while on antipsychotics.

Case presentation
A 53-years-old Caucasian woman (BMI 32.7 kg/m²) 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
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 diagnosed 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/l 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 hydration, 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.

Introduction
Although psychiatric manifestations in the form of delirium, confusional states, and psychosis have been commonly reported in relation to hyperglycemia, 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 unit with these complaints: Vomiting, epigastric pain, Polyuric-polydipsic syndrome, fatigue, agitation. Familial history negative. Objective 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 49/U/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, Granulocytes 80.2%, lymphocytes and monocytes normal. RBC 3.14 million/mm³, HGB 10.9, PLT 187/mm³, MCV microlitre/100 (80–97), urine analyses: negative acetone, albumin 2.64 g/leukoocyte filled areas, 4–5 erythrocytes/field. Imagery examination: Abdominal ultrasonography, hepatosteatosis, liver with large dimension 158 mm, rough echo structure, porta 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 psychiatric treatment with Librium 10 mg 3x1 tb, haloperidol 2x10 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
Selfe 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 to a hobby to psychiatric ailments, 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 (≥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, investigatory 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 in the cyto genetic 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±7.02 years. In the patient group, 39 participants with a mean age of 52.15±6.21 years were included in the study. In the control group, average FGF21 measurement was 121.35±88.4 pg/ml while FGF21 measurement in the patient group was 171±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, 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 primarily 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 SR90495 are commonly used for research the rescue potential of mutant AVPR2s. We aimed to show the rescue potential of SR121463A and SR90495 as a pharmacological chaperones in treated AVPR2 mutants (G12E, R68W, ΔR67-G69/G107W, R85M, R106C, V162A, T273M). These mutants were previously described and functionally analysed by our group. After treatment with SR121463A and SR90495, 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 SR90495. In conclusion, as a therapeutic target, SR121463A and SR90495 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 SR90495. 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. In vivo strategies have been studying and using dDAVP nasally is one of these strategies. In vivo 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 as pharmacological chaperones to rescue of mutant AVPR2s
were selected as pharmaceutical 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 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. Our study was supported by The Scientific and Technological Research Council of Turkey (TBAG Project number 2163S304). 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 polyglandular 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 polyglandular 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 insulin infusion and fluid replacement therapy. Laboratory test results as follows glucose: 114 mg/dl, HBA1C: 11.8%, TSH >0.005 mIU/ml, FT4: 0.98 ng/dl, FT3: 4.8 pg/ml, anti-TPO: 600 IU/ml, anti TG: 341.2 IU/ml (0–115), as follows glucose: 114 mg/dl, HBA1C: 11,8%, TSH 0.005 uIU/ml, FT4: 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 insulin 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 syndrome (46XO DEL (X) Q13), ANA, celiac antibody, anti-partial 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 Mineralocorticoid Receptor (MR). It is the selective presence of isoform 2 of 11beta-hydroxysteroid dehydrogenase (11BHS) 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 11BHS 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 11BHS. 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 6 g 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 rhythm 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.

DOI: 10.1530/endoabs.56.EP96

**EP97**

Stein leventhal syndrome: a report of two cases

Amina Abdi

E.P.S.P Ghoualem Oran, Oran, Algeria.

**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 clinical 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 hyperinsulinaemia 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
Amina Abdi
E.P.S.P Ghoulame Oran, Oran, Algeria.

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 ampulla.

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 duodenopancreatectomy 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.

DOI: 10.1530/endoabs.56.EP98

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 interdisciplinary 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 adenomas and disorders commonly associated with them
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Background
The prevalence of pituitary adenomas (PA’s) 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 growth-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 (NFP), prolactin (PRL+) or growth 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 NFP 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 65.5% 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 unchanged factors that might predict the positive outcomes like the age, a smaller size of the tumor or a lower 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 ~ 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 ocular defect 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 transphenoidal endoscopic cystic 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 corticotrophic deficiency (cortisol: average 65 ng/ml and ACTH: average 4 pg/ml) were confirmed in all sporadic cases while the gonadotropin and thyroid axes were spared. On the contrary; in familial cases they were consistently affected (FSH: mean 1.1 mIU/ml, LH: mean 2 mU/ml, E2: <3 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 remaining cases, including one case with abnormal X chromosome structure. No correlation was found between the chromosomal 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, Hhex1, 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.

DOI: 10.1530/endoabs.56.EP103

EP104
Evaluation of differential diagnosis and treatment stages of TSH-secreting pituitary microadenoma which responding to cabergoline therapy
Soner Cander, Ozen Oz Gul, Elif Gunes, Canan Ersoy & Erdinc Erturk
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Introduction
High thyroid hormone levels with unsuppressed TSH (atypical hyperthyroxinemia) is one of the difficult endocrinologic conditions. When the conditions leading to euthyroid hyperthyroxinemia 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 mU/ml (0.350–4.940), 5.2 pg/ml (1.71–3.71) and 1.84 ng/dl (0.70–1.48) respectively. Patient subsequently losted two months ago and similar findings were found in the tests. Pituitary MRI showed a pituitary adenoma on the left side and 7x4.4 mm in size. Atrial fibrillation was present in the clinic, SHBG level was 62 nmol/l (10–57). In the THR 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 (≤ 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 THR. 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, hypophysal hyperplasia can be seen in THR, heterogeneity in clinical findings, genetic testing can not always be done or result is negative in 10% of patients with THR, 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.

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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 drug 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 progestrone 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 sinuses. Monitoring of the patient without medication is continued.

Conclusions
Multiple pituitary adenomas are defined as simultaneous, morphologically or immunocytoologically, 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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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, nonsmoker, 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 hysterectomy, sleep apnea and multinodular goiter with hypothyroidism. Clinical examination showed acromegalic facial appearance, bilateral alinar 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 0.70x0.5 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 recommendation. Thus, we confirmed the current inactive status of the acromegaly and the absence of pituitary gonadotrophin and thyrotrphin 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 occurrence of both autoimmune and neuroendocrine pathway in the same patient.

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**EP109**

**Ectopic clival prolactinoma with empty sella in a patient using antipsychotic**

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²Mersin University Radiology, Mersin, Turkey.

Prolactinoma is the most common cause of chronic hyperprolactinemia and drugs that rise serum prolactin levels have been ruled out. Although 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 prolactin levels, suggested the diagnosis of an ectopic prolactinoma. Because of the rise serum prolactin levels, the patient was treated with the drug of choice for treatment of hyperprolactinemia.

**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 and paroxetine.

**Conclusion**

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. Cabelgine was used in 92% and Bromocriptine was used in 8% patients for treatment of hyperprolactinemia.

**Table 1** Demographic data of the enrolled acromegalic patients.

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>60</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Age (mean ± SD) years</td>
<td>46.35 ± 10.81</td>
<td>46.3 ± 10.9</td>
<td>46.3 ± 10.8</td>
</tr>
<tr>
<td>Duration (mean ± SD) years</td>
<td>10.44 ± 6.5</td>
<td>10.5 ± 6.7</td>
<td>10.4 ± 6.5</td>
</tr>
<tr>
<td>Minimum duration years</td>
<td>1 month</td>
<td>6 month</td>
<td>1 month</td>
</tr>
<tr>
<td>Maximum years</td>
<td>30 years</td>
<td>30 years</td>
<td>20 years</td>
</tr>
</tbody>
</table>

**Table 2** Those harboring micro or macroadenoma.

<table>
<thead>
<tr>
<th>Patients with mutation</th>
<th>Patients without mutation</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Males number (%)</td>
<td>14 (50%)</td>
<td>18 (56.25%)</td>
</tr>
<tr>
<td>Females number (%)</td>
<td>14 (50%)</td>
<td>18 (43.75%)</td>
</tr>
<tr>
<td>Macroadenoma</td>
<td>22 (78.5%)</td>
<td>25 (78.12%)</td>
</tr>
<tr>
<td>Microadenoma</td>
<td>6 (21%)</td>
<td>7 (21.87%)</td>
</tr>
<tr>
<td>Trans-sphenoidal</td>
<td>8 (28.5%)</td>
<td>15 (46.87%)</td>
</tr>
<tr>
<td>No hypophysectomy</td>
<td>20 (71.4%)</td>
<td>17 (53.12%)</td>
</tr>
</tbody>
</table>

**Table 3** The response rate to octreotide in acromegalic patient and with.

<table>
<thead>
<tr>
<th>Patient with no mutation</th>
<th>Patient with mutation</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Full responder</td>
<td>18 (56.25%)</td>
<td>14 (50%)</td>
</tr>
<tr>
<td>Partial responders</td>
<td>12 (37.5%)</td>
<td>7 (25%)</td>
</tr>
</tbody>
</table>

**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. Cabelgine 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. Cabelgine 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 octreotide**

Abbas Rahmah¹, Assel Sami² & Wathiq Abbas³
¹National Diabetic Center, Baghdad, Iraq; ²Genetic Engineering and Biotechnology Institute, Baghdad, Iraq.

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.

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>60</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Age (mean ± SD) years</td>
<td>46.35 ± 10.81</td>
<td>46.3 ± 10.9</td>
<td>46.3 ± 10.8</td>
</tr>
<tr>
<td>Duration (mean ± SD) years</td>
<td>10.44 ± 6.5</td>
<td>10.5 ± 6.7</td>
<td>10.4 ± 6.5</td>
</tr>
<tr>
<td>Minimum duration years</td>
<td>1 month</td>
<td>6 month</td>
<td>1 month</td>
</tr>
<tr>
<td>Maximum years</td>
<td>30 years</td>
<td>30 years</td>
<td>20 years</td>
</tr>
</tbody>
</table>

Table 2 Those harboring micro or macroadenoma.

<table>
<thead>
<tr>
<th>Patients with mutation</th>
<th>Patients without mutation</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Males number (%)</td>
<td>14 (50%)</td>
<td>18 (56.25%)</td>
</tr>
<tr>
<td>Females number (%)</td>
<td>14 (50%)</td>
<td>18 (43.75%)</td>
</tr>
<tr>
<td>Macroadenoma</td>
<td>22 (78.5%)</td>
<td>25 (78.12%)</td>
</tr>
<tr>
<td>Microadenoma</td>
<td>6 (21%)</td>
<td>7 (21.87%)</td>
</tr>
<tr>
<td>Trans-sphenoidal</td>
<td>8 (28.5%)</td>
<td>15 (46.87%)</td>
</tr>
<tr>
<td>No hypophysectomy</td>
<td>20 (71.4%)</td>
<td>17 (53.12%)</td>
</tr>
</tbody>
</table>

Table 3 The response rate to octreotide in acromegalic patient and with.

<table>
<thead>
<tr>
<th>Patient with no mutation</th>
<th>Patient with mutation</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Full responder</td>
<td>18 (56.25%)</td>
<td>14 (50%)</td>
</tr>
<tr>
<td>Partial responders</td>
<td>12 (37.5%)</td>
<td>7 (25%)</td>
</tr>
</tbody>
</table>
Table 4 The response rate to octreotide.

<table>
<thead>
<tr>
<th></th>
<th>Patient with A mutation</th>
<th>Patient with non A mutation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Response Full responder</td>
<td>8 (40%)</td>
<td>6 (75%)</td>
<td>0.2094</td>
</tr>
<tr>
<td>Partial responders</td>
<td>6 (30%)</td>
<td>1 (21.5%)</td>
<td>0.8722</td>
</tr>
<tr>
<td>Non responders</td>
<td>6 (30%)</td>
<td>1 (21.5%)</td>
<td>0.8722</td>
</tr>
</tbody>
</table>

Table 5 Shows the variable data of those with type A and non A.

<table>
<thead>
<tr>
<th></th>
<th>Mutation A</th>
<th>Non A mutation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Males number (%)</td>
<td>10 (50%)</td>
<td>4 (50%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Females number (%)</td>
<td>10 (50%)</td>
<td>4 (50%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Macroadenoma</td>
<td>16 (80%)</td>
<td>6 (75%)</td>
<td>1.8034</td>
</tr>
<tr>
<td>Microadenoma</td>
<td>4 (20%)</td>
<td>2 (25%)</td>
<td>0.8982</td>
</tr>
<tr>
<td>Hypophysectomy</td>
<td>7 (35%)</td>
<td>1 (12.5%)</td>
<td>0.6735</td>
</tr>
<tr>
<td>No hypophysectomy</td>
<td>13 (65%)</td>
<td>7 (87%)</td>
<td>0.3046</td>
</tr>
</tbody>
</table>

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 undergo 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 30 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 1 and cholecystectomy was preformed for 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 vs 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
Dan Alexandru Niclelescu1, Ramona Dobre1, Anda Carageaegheorgheopol2, Nicoleta Popescu1 & Catalina Potana1
1Department of Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 2Department of Pituitary and Neuroendocrine Disorders, C. I. Parhon National Institute of Endocrinology, Bucharest, Romania; 3Research Laboratory, C. I. Parhon National Institute of Endocrinology, Bucharest, Romania; 4Biochemistry Laboratory, C. I. Parhon National Institute of Endocrinology, Bucharest, Romania.

Background
Growth hormone, age, sex, genetics or nutrition status play an important role in insulin-like growth factor 1 (IGF-I) 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, Saluggia, 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-I correlation Default (r, p) were −0.6793x + 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-I was confirmed.

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EP114
Hyponatremia as a first symptom of hypopituitarism due to pituitary metastasis of gastric cancer: Case study
Agnieszka Zwolak1, Marcin Lewicki2, Ewa Tywanek3, Joanna Swirska1, Marta Dudzińska1 & Jerzy Tarach3
1Chair of Internal Medicine and Department of Internal Medicine in Nursing, Medical University of Lublin, Lublin, Poland; 2Chair and Department of Epidemiology and Clinical Research Methodology, Medical University of Lublin, Lublin, Poland; 3Chair and Department of Endocrinology, Medical University of Lublin, Lublin, Poland.

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 tubarele without HER2 amplification), treated with capetzabin, epirubicin, and oxalplatin 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, gonadotropin 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 x 15mm mass infiltrating sella turica 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.

EP115
Macroprolactinemia diagnosed in a patient evaluated for primary infertility
Claudia Nogueira¹, Filipe Cunha¹, Ivan Ferreira¹ & Joana Mesquita²
¹Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal; ²Centro Hospitalar de Entre o Douro e Vouga, Santa Maria da Feira, Portugal.

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
35-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, OG 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 mU/l (0.27–4.20), free T4 20.9 pmol/l (11.7–21.7), FSH 7.7 mIU/ml, LH 5.42 mIU/ml, estradiol 65.6 ng/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 suspicion of asymptomatic hyperprolactinemia. 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
Roxana Maria Tudor, Hannah Forde, Amar Agha, Clare Faul & Molhsen Javadpour
Beaumont Hospital, Dublin, Ireland.

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 sphenoid-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 headache, 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.

DOI: 10.1530/endoabs.56.EP116

EP117
GH/TSH secreting adenoma: a clinical case report: GH/TSH secreting adenoma: a clinical case report
Tatiana Tarasova, Alexander Lutsenko, Elena Przhivalkovskaya, Ekaterina Pigarova, Larisa Dzeranova, Anatoly Tsiulpakov & Ivan Dedov
Endocrinology Research Centre, Moscow, Russian Federation.

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 29.0 pmol/l, free T3 10.4 pmol/l, TSH 6.3 mIU/l, IGF-I 327.1 ng/ml (less than 280.0), beta-crosslaps 0.71, SSBG 200.0 mmol/l (less 110.0). Short-acting octreotide treatment resulted in normal-ization TSH and IGF-I. 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, CDKNIB, PRRKAI, GNAS, AIP, SDHA, SDHB, SDHC, SDHD, PRCA, CDKN2C, CDKN2A, POU1F1, PTTG2), which revealed following changes: SDHA: NM_0004166: exom2c:G1002A:p.A334A, rs144252500, MAF 0.002; DICER1:NM_177438:exon2c:200G:p.G7R, 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.

DOI: 10.1530/endoabs.56.EP117
EP118
Antiphospholipid syndrome and pituitary necrosis
Manel Jemel, Hanene Sayadi & Ines Khochtali
Fattouma Bourguiba University Hospital, Department of Endocrinology, MONASTIR, Tunisia.

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 nodular field, a central facial paralysis and monoparesis right upper limb. In biopsy, it has a hyperprolactinemia to 40 times normal and central hypothyroidism. Anticardiolipin antibodies were positive. Synchon 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.
DOI: 10.1530/endoabs.56.EP118

EP119
A rare emergency case in endocrinology: pituitary apoplexy
Suheyla Gorar, Cezmi Cagri Turk, Tolga Gediz & Gulsah Inal
Antalya Training and Research Hospital, Antalya, Turkey.

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 menstrual 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 mU/ml (0.3–5.8), LH: 2.77 mU/ml, FSH: 6.15 mU/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 hormogram 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 consulted 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 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. Sclar 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.
DOI: 10.1530/endoabs.56.EP120

EP121
Emotional disorders in patients with tumours of diencephalic localization
Yuliya Sidneva, Liudmila Astafyeva, Oleg Zaitsev, Pavel Kalinin, Maxim Kutin & Irina Klochkova
N.N. Burdenko National Medical Research Center of Neurosurgery, Moscow, Russian Federation.

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 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 moodiness, 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.
DOI: 10.1530/endoabs.56.EP121

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 tests 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. Sclar 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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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 17x16x15 mm of residual macroadenoma on pituitary MRI with level of GH 17.5 ng/ml and IGF-1 422 mg/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 approximately 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 21900 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 subsclinal 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 21900 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
During the screening research at 21 the subclinical Cushingoid was taped. All patients with subsclinal 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%).

DOI: 10.1530/endoabs.56.EP123


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 21900 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/m2) 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/m2) 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) 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 normalized 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 ‘panhypopituitarism’*  
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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 colon polyps. His medications included amlopidine, 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 a 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 depletion 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 multicellular 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 pallate which the patient used to have before, bilateral visual acuity improved to 10/10. Visual chum 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 urges 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 all been 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 chiasms. Bitemporal adenoma was found on hypophysis MR. The adenomatous cavernous sinus showed an adenoma and immunohistochemical findings were consistent with gonadotropinoma.

Conclusion
In macroadenomas without clinical function, it is recommended to apply surgical treatment to visual field deficit or loss, ophthalmoplegia, optic chiasmal pressure, and hormone insufficiency. 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, it 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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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 75 μg. Since elevated TSH up to 6.3 mIU/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 mIU/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 mIU/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. Transsphenoidal adenectomy was performed in the Department for neurosurgery without post-operative complications. Pathohistological examination with immune-histochemical staining confirmed growth hormone secreting pituitary adenoma. Post-surgical hormone profile showed TSH 0.88 mIU/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 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

Galactorrhea, 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, galactorrhea 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 palpuble right thyroid nodule. She was investigated by means of a pituitary protocol 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 galactorrhea subsided on cabergoline which was stopped at 6 weeks. She then reported bilateral galactorrhea 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
We hereby 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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Relevance
Prolactinomas are 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 dissuaded into 1 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 oligoamenorrhea, up to 80% also observe galactorrhea. Involuntary 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 macroprolactinoma, 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.

Methods
Data was collected and analysed on an encrypted excel sheet. University College Hospital Galway (UCHG). Charts were ordered, reviewed and Online Patient Correspondence System was used to identify patients with TS in University College Hospital Galway.

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 continual management. Turner’s syndrome in University College Hospital Galway (UCHG). Charts were ordered, reviewed and Online Patient Correspondence System was used to identify patients with TS in University College Hospital Galway.

Results
Fourty five postmenopausal subject and 39 healthy participant were included in the study. We found that in postmenopausal group, disulphide (P<0.004), total thiol (P<0.003), total thiol/native thiol (P<0.004), disulphide/native thiol (P<0.004) were higher than the control group. 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, 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.
Our study supports the hypothesis that decreased albumin and inflammation might be the major cause of oxidative imbalance. This study showed that postmenopausal phase is associated with oxidative stress.

**Conclusion**

Our study supports the hypothesis that decreased albumin and inflammation might be the major cause of oxidative imbalance. This study showed that postmenopausal phase is associated with oxidative stress.

**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 0.4–4 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/FSH > 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 function 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 ovarioectomized 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 flow rate was evaluated using a laser Doppler system at 7, 0, 7, 14, 21 days after hind-limb ischemia. The serum profiles of angiogenic 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 angiogenic factors including ET-1, ANGPT-1 and IGFBP-3, whereas, the inflammatory cytokines, TNF-α, IL-6 and IL-1ß 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%). 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 amenorrhoea 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, Xi(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 or female 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 known 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 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 obser 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 assessment (HOMA-IR) which is an index of insulin resistance is statistically significantly higher in PCOS patients (P<0.01). In the hormonal evaluation of the subjects the level of dehydroepiandrosterone-sulphate (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 intraperitonially treated with physiologic 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 (GPO) 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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**EP147**

**From aneuploidy to cryptoid: 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.

**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 with those born to women without AITD.

**EP149**

**“Gym and anabolists”**

Pilar Rodriguez, Catalina Diaz, Isabel Rebollo, Irene Gonzalez & Maria Jose Lopez Hospital Juan Ramon Jimenez, Huelva, Spain.

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 PA's 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 tumor in the left breast; hair loss at the frontal level, in analical 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 (Decabolin, 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, Band cortisol 1640, TSH 2.29 mU/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.

**EP150**

**Amenorrhea and benign intracranial hypertension as an effect of anipsychotic therapy in a patient with schizophrenia**

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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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**EP150**

**Amenorrhea and benign intracranial hypertension as an effect of anipsychotic therapy in a patient with schizophrenia**

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**EP150**

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Conclusion

The occurrence of autoimmune thyroid disease in pregnant women increases birth weight of their children.

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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 hyperhidrosis and diabetes was found in 73% of cases. Hirsutism occurred 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/progesterone 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/m². 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 before the age of 9 years in boys. Central PP has an idiopathic origin in up to 95% of girls while in up to 50% of males. The diagnostic and the management of PP can be particularly 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 mU/mL, which was multiplied by 14 after GnRH administration. Estradiol level 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 mU/mL, and its peak concentrations after GnRH agonist stimulation was respectively 6.5 and 12 mU/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 cm 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, 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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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%, CHF19%, 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 thyroids 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 frequent 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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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 spaniomenerorhea, 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 antiperoxidase 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 hyperprolactactinemia (69 μg/L). A pituitary magnetic resonance imaging (MRI), requested in order to explore this hyperprolactactinemia, 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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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 autoimmune disease, it may be associated with other autoimmune 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 IPGIMER 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 long 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 myopathy may suppress inflammatory myopathy and diarrhoea itself can be a feature of thyrotoxicosis. There is scarcity of cases shown association among these three autoimmune diseases. 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 ul/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 ul/ml, standard deviation: 6.88. Therefore, the upper limit should be 21.89 ul/ml.

Discussion

Based on 34 ul/ml cut-off limit, we registered 1750 patients with HT (higher ATPO), 205 patients with only high antityroglobulin thyroiditis (ATG-T) (low ATPO), 126 patients with idiopathic myxedema (hypothyroidism, lower ATPO/ATG, and inflammatory ultrasound signs) and 1875 patients controls, with other thyroid diseases (mostly thyroid nodules). Considering ATPO cut-off as 21.89 ul/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 ul/ml and not 34 ul/ml. 2. Based on 23 ul/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 aggravate 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/min), 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 ul/ml), markedly increased level of free thyroxin (FT4) - 100 n–12–22 pmol/l), free triiodothyronine FT3-6.5–(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 < thyroid inferno >. Patient was diagnosed Grave’s thyrotoxicosis. Follow up after 3 weeks of treatment with Thyrozol 50 mg per day. Anaprilin 160 mg 4 times per day, Miratazpine 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) FT3 4.5 ng/ml (n–0.8–2.0 ng/ml). Treatment continued with same daily dose of Thyrozol and Anaprilin 120 mg, Miratzapine 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(6) -<105 pmol/l. Hepatitis are checked: Hepatitis C and A were negative.HBsAg 1081.55 S/CO. HBV quantitative 0.18 IU/ml. It appeared patient had teeth removal one year ago. After consultation with infectionist anti viral treatment didn’t prescribed. Taiking in account presence of hepatitis B, alcoholism, hepatotoxicity of Thyrozol, high level of anti-R TSH, Thyrozol canceled and patient prepared for total thyroidectomy as Radiosine therapy is unavailable in Armenia. Patient was given lyugol solution for 10 day 7 drops 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/L, ALAT-35 U/l, 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 endemiy 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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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 receptor antibody was 0.49, TGA (˃300 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 suprse 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 was seen. Primary hypothyroidism was diagnosed. TSH level was depressed. (TSH: 47.64 mIU/ml, FT4: 1.15 ng/dl). The height of the pituitary was measured as 6.6 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. 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.

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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 goiter. 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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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 (92.9%) 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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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 131I. 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 lyed with isoechoic nodes, about 10% of which had ultrasound signs of cystic degeneration. The median free T4 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 diarrhea. 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 high blood pressure 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 a 24-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/m², 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 (KC) 1060 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.72–407.4), 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 periodic paralysis.

Hypokalaemia. Treatment: Thiamaol 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
TPP is potentially lethal condition, which is difficult to diagnose, thus for all patients with unclear etiology 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 dermopathy 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 mU/l (0.45–4.5 mU/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 mU/l (both positive), and anti-acetycholine 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. Why he performed a TC scan. TC revealed an anterior homogeneous mediastinum mass with 39 ×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 hyperplastic 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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Familial dysalbuminaemic hyperthyroxinaemia, a thyroid conundrum

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Background
Familial dysalbuminaemic hyperthyroxinaemia (FDH) is an interesting auto-
sonal dominant condition that is associated with euthyroid hyperthyroxinaemia, whereby patients remain euthyroid but laboratory value will show high free
thyroxine (fT4) level. It is caused by mutations in ALB (albumin) gene that increase affinity of albumin for thyroxine (T4). The usual thyroid assay will show a
spurious 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 T4, 30.4 pmol/l and triiodothyronine (T3) level of 5.5 pmol/l with a normal thyroid
albumin gene, R242H in keeping with FDH. We stopped carbimazole and
function test.

Her carbimazole was further increased to 20 mg. Her repeat blood test then
collagen bundles. Dermopathy was successfully treated topical corticosteroids.

revealed accumulation of mucin in reticular dermis leading to separation of
methimazole 2 tb/day and TRab was 1.3 IU/l (at the time of diagnosis it was
divided doses). The patient was euthyroid at the time of evaluation with
moderate orbitopathy and received iv steroid therapy (4.5 gr prednisolone in
presented a firm and non-depressible consistency. Patient had a history of active

At the dermatological examination, a plaque with a shiny surface, measuring five

Case 1
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. Radiative 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
periostial 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 have a lesion and the diagnosis is equivocal.

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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 ophthalmopathy. The diagnosis
requires physical examination and clinical suspicion and in doubtful cases biopsy
can 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. Radiative 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
periostial 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 have a lesion and the diagnosis is equivocal.

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BRCAl mutations and polymorphisms 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 mastopathy, we looked for BRCAl mutations in women wit and without goiter

Methods
One hundred and fifty two women-96 with and 56 without nontoxic goiter were examined in 2017. In US examination we calculated the volume of the thyroid gland and volume of nodules. Blood samples for BRCAl were taken, ex505 - p.Cys61Gly; ex 11 polymorphisms K1183R, mutations: c.3819delc, c.3875delc, 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 mL 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 above 20 ng/mL. We found no one pathogenic mutation in any group, and polymorphisms 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 BRCAl 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 of our research there is no increased incidence of BRCAl 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 collateral nodules, with metastases in supra isthmic and left supraclavicular lymph nodes. A complement by iatrogeny was performed, with bilateral cervical lymph node dissection, which revealed: bilateral jugular chain metastases, three metastases in the recurrent chain with capsule invasion. The medullar 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, intraparanchymal and subpleural lung nodules, bilateral auxillary 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 prelbral 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. It runs a various course and many times during its natural course permanent hypothyroidism may ensue.

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 FT3, 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 hypothyroidism.

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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.

Objectives
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 T4 <0.1 ng/ml, Total T4 = 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 mU/ml. She was admitted to the clinic when 1.7 years referring language delay. Initial investigation: TSH = 1.3 mU/ml and total T4 = 5.4 mg/dl. Significant improvement in language development occurred after thyroxin replacement. Serum TSH and total T4 during treatment were 0.6 mU/ml and 7.6 mg/dl and change to 1.5 mU/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 encoding 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 Sjogren 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, right upper lobectomy was performed. The histopathological 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 foci of struma nodosa colloides were found. Further treatment with J131 was complicated by anemia, leukopenia 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 postoperative examination. If so, we do not know why the symptoms appeared only after 11 years, or whether the treatment of Sjogren’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 occurrence 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 hurthic cell adenoma and parathyroid adenoma
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Introduction
Hurltie 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 Hurthle 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 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.

Conclusions
We presented a case that of a 50-year-old woman with neck swelling. 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.

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EP179

Prognostic factors affecting neck lymph node 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 metas: 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 measured at diagnosis of lymph nodes metastasis: 52.95 ± 174.40 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 GY.

† TG measured at diagnosis of lymph nodes metastasis: 52.95 ± 174.40 ng/ml and 17.5% of patients had positive anti-TG.

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 isoetic 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.

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 antithyroperoxidase autoantibodies (ATPO) and/or antithyroglobulin autoantibodies (ATG) and their destructive process on thyroid cell. The diagnostic uses specific and very characteristic ultrasonic 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 ATG's?

Method

i) ATPO and ATG levels were analyzed in accredited Buckarest laboratories. ii) We considered HT those patients with high ATPO/ATG levels, cut off over 100 u/ml. iii) FT4 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

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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 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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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 abnormalities 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 outpatient 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 nonotoxic 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 pathophysiology 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 ultrasonography 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 (T4), triiodothyronine (T3), 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 TSH and free T4 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 levotyroxine post-surgical. Literature review is made.

Case 1
Age 28, gestational age = 16.2 weeks. Diagnosis before pregnancy. TSH = 0.000 uIU/ml, free T4 = 7.77 ng/dl. At physical examination with tachycardia, hypertension, trembling limbs and aortic heart murmur. 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 = 2.4 uIU/ml, free T4 = 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 T4 = 1.09 after pregnancy.

Case 2
Age 21 years, gestational age = 17 weeks. Diagnosis before pregnancy. TSH = 0.003 uIU/ml, free T4 = 6.5 ng/dl. At physical examination with tachycardia, hypertension, trembling limbs and auricular fibrillation. Thyroid ultrasonography with multinodular goiter Triads 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 T4 = 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 T4 = 1.2 after pregnancy.

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EP188
Comparison of results of cytological and histological 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±9.2 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, follicular 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, follicular 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%) - follicular proliferative nodes in different degrees, in 1 (20%) - papillary cancer. The sensitivity of the cytomorphological method of diagnosis of ‘nodal 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 preparative 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 symptoms 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) discussions as possible predicting of thyroid papillary microcarcinoma (MPTC)
Liana Gogiashvili, Tamuna Gvianishvili & Zurab Tsagareli
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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 thyrocyes 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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